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# ARCHIVES OF OPHTHALMOLOGY

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NUMBER 1

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## INFLUENCE OF GRENZ RAYS ON CELL DIVISION AND WOUND HEALING IN THE CORNEAL EPITHELIUM

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AND

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NEW YORK

THE EYE is subjected to many forms of radiation for the purpose of treatment or diagnosis. Among these are the grenz rays, which have been used extensively for the past fifteen years. They are soft rays of 1 to 4 angstrom units, intermediate between the ultraviolet and the usual roentgen rays,<sup>1</sup> and have some biologic properties in common with both of these, more familiar, forms of radiant energy, but do not penetrate very deeply into the tissues of the eye.<sup>2</sup>

Grenz rays have been found of value in the treatment of superficial ophthalmic conditions, such as corneal ulcer or episcleritis, and are considered to be safer than ordinary roentgen rays. The clinical application of this form of radiation has been extensively reviewed.<sup>3</sup> Krasso<sup>4</sup> reported histologic changes in the cornea caused by heavy single irradiations of the rabbit eye. Gallardo, Pfeiffer and Thompson<sup>5</sup> found that

From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University

1 Bucky, G. Grenz Ray Therapy, translated by W J Highman, New York, The Macmillan Company, 1929

2 Sagher, F, and Sagher, E. Absorption of Infra-Roentgen (Bucky) Rays of Various Qualities by the Anterior Portions of the Eyeball, *Arch Ophth* **30** 43-53 (July) 1943

3 (a) Pfeiffer, R L. Treatment of Diseases of the Eye with Grenz Rays, *Arch Ophth* **21** 976-985 (June) 1939 (b) Ellinger, F. The Biologic Fundamentals of Radiation Therapy. A Textbook, English translation by M Lenz, New York, Elsevier Pub Co, 1941

4 Krasso, I. Experimentelles und Histologisches über den Einfluss einer einmaligen Bestrahlung mit Bucky's Grenzstrahlen auf das gesunde Kaninchenauge, *Ztschr f Augenh* **70** 237-256, 1930

5 Gallardo, E, Pfeiffer, R, and Thompson, R. Grenz-Ray Treatment of Experimental Infection of the Cornea, *Am J Ophth* **23**:41-47, 1940

infections produced by intracorneal injections of staphylococci healed more rapidly if treated with grenz radiation. These authors had previously reported that the local formation of antibodies was increased by grenz irradiation.<sup>6</sup>

The effect of ordinary roentgen radiation on cellular proliferation is well known, but that of the grenz rays apparently has not been reported, except for a note by Politzer and Zakovsky<sup>7</sup> on their effect on cell division in urodele larvae. In view of the use of grenz rays on the eye, an investigation of their effect on cell division in the intact, and on regeneration of the injured, corneal epithelium seemed advisable.

#### METHOD

Male rats, of the Sherman strain, 4 to 6 weeks of age and weighing about 100 Gm, were used in these experiments. In the first series 57 animals were used. With the rat under pentobarbital anesthesia, one eye was given a single treatment of 410 r,<sup>7a</sup> a dose which may be used clinically at three to four day intervals.<sup>8</sup> The rats were killed by decapitation at stages of from six hours to twelve days after irradiation. Litter mates were used throughout this study and were distributed so that animals in one litter were autopsied at various periods after receiving the grenz ray treatment. Four animals were used in each group.

The eyes were fixed in a mixture of solution of formaldehyde USP and alcohol and the corneas prepared as flat whole mounts according to the method of Buschke, Friedenwald and Fleischmann,<sup>8</sup> with minor modifications. The number of mitoses seen in two to three strips extending across the greatest width of the cornea was counted. The size of the strip was regulated by an Ehrlich stop, a 4 mm square was placed in a  $\times 10$  ocular and used with a  $\times 43$  objective. The number of mitotic figures observed in the irradiated (right) eye was compared with the number found in the corresponding epithelial area of the untreated, control (left) eye of the same animal. The difference was expressed as the percentage of the control value. Seventy-five to 150 mitotic figures were counted in the area studied in the normal eyes.

The effect of grenz irradiation on regenerating epithelium was investigated in 29 animals. The injury produced was a standard thermal burn inflicted on the cornea of both eyes with a Shahan thermophore heated to 71 C. The tip of the thermophore was shaped to fit the rat's cornea and made a burn 15 mm wide, which extended horizontally across the cornea. The area of the burn was one-fourth to one-third that of the cornea. The epithelium was completely destroyed, but the superficial portion of the stroma was left intact. The burned cells sloughed

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6 Thompson, R, Pfeiffer, R, and Gallardo, E, Jr. Stimulation of Local Antibody Formation in Cornea by Grenz Rays, *Proc Soc Exper Biol & Med* **36** 179-181, 1937.

7 Politzer, G, and Zakovsky, J. Vergleichende Untersuchungen über die Wirkung der Bucky- und der Röntgenstrahlen auf die Zellteilung, *Strahlentherapie* **42** 165-170, 1931.

7a The factors were 10 kilovolts, 4 milliamperes, no added filtration (half value layer, 0.04 mm aluminum), target skin distance, 8 cm, circular portal, 8 mm in diameter.

8 Buschke, W, Friedenwald, J S, and Fleischmann, W. Studies on the Mitotic Activity of the Corneal Epithelium. Methods, Effects of Colchicine, Ether, Cocaine and Ephedrin, *Bull Johns Hopkins Hosp* **73** 143-167, 1943.

within two hours, and after a latent period of about six hours the epithelial cells began to move over the denuded area. The area of the burn was completely covered with a thin layer of cells in fourteen to fifteen hours, but the normal thickness was not restored for several days.

In the experiments on the effect of grenz irradiation on this process, one eye was irradiated, as in the other experiments, and the two eyes were burned equally. Pentobarbital anesthesia was used during irradiation and ether anesthesia when the burns were inflicted. The time between irradiation and injury varied from one hour to ten days. Twelve to fifteen hours after the corneas were burned the rats were killed and the eyes fixed for histologic study. When the eyes were in 80 per cent alcohol, the unhealed portion of the burn could be seen precisely with the aid of a dissecting microscope. Drawings of the unhealed area of the burn were made with the camera lucida. Untreated burns were nearly healed at the twelve hour stage, and completely so at the fifteen hour stage. The areas of the drawings of the irradiated and the control burns were measured with a planimeter and the values compared. The corneas were then stained and the mitotic figures in the regenerating epithelium counted, as in the experiments with the intact corneas.

### RESULTS

Irradiation of the rat cornea with grenz rays caused a precipitous drop in the frequency of mitotic figures in the corneal epithelium. The data obtained are presented graphically in figure 1. Six hours after irradiation no mitotic figures were observed in the corneal epithelium of the irradiated eyes. Fifteen hours after irradiation a few cells were to be seen undergoing division, but the number still averaged 78 per cent less than that in the control eyes of the same animals. Mitosis remained greatly depressed for five days after a single irradiation, but on the sixth day the number of figures seen in the irradiated cornea had returned to normal. No difference between the control and the irradiated eyes was noted in any case of the six day group. Some indication of an increase in mitosis in the irradiated eye was noted on the eighth day, but the number of dividing cells was normal in both the irradiated and the control eyes on the tenth and twelfth days after irradiation, when the experiment was terminated. The frequency of mitotic figures in the nonirradiated, control eyes remained at normal levels in all the experiments.

In one experiment the rats were given two irradiations each with the same dose as that used in the other experiments. The second irradiation was made three days after the first, and the animals were autopsied on the third day after the second irradiation. Mitosis was conspicuously inhibited in the irradiated corneal epithelium. Since the inhibiting effect of a single irradiation had disappeared by the sixth day in the first experiment, it appears that the inhibition could be maintained by the second irradiation.

Although these data show that the grenz rays inhibit mitosis, they given no indication at which point the block in that process occurs. For



this reason, the number of figures in various stages of mitosis were determined in control and in irradiated eyes. All figures were classified as prophase, metaphase or telophase. The proportion of each stage observed in the irradiated and in the control epithelium are shown in figure 2. The proportions of figures found in these three stages were similar to those reported by Kaufmann and associates<sup>9</sup>. The distribution of phases noted in normal eyes was almost identical with that observed in the irradiated eyes. This indicates that the radiation acts at some stage prior to the entrance of the cell into the actual division process. The cells are prevented from entering the prophase, but once started the process of division goes on normally.

A greatly reduced dose of grenz rays was applied to two groups of rat eyes by shortening the exposure from sixty to ten and five seconds, respectively. Twenty-four hours after irradiation the average number of mitotic figures was reduced slightly in the ten second exposure group

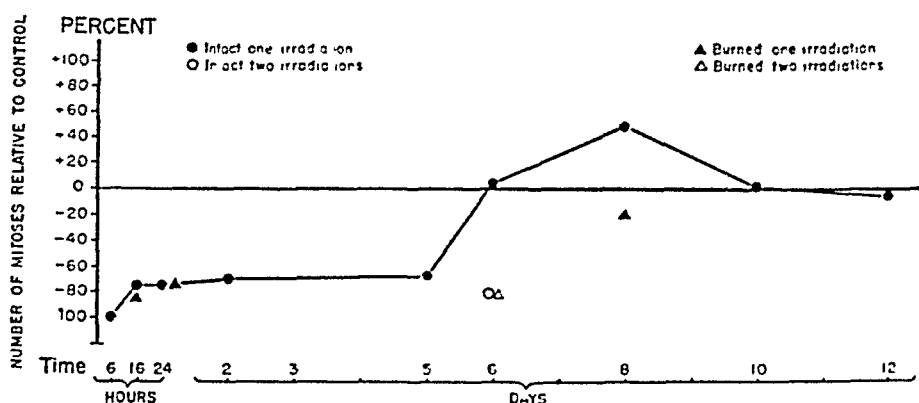


Fig 1—Decrease in frequency of mitotic figures in the rat cornea after irradiation with grenz rays

(—19 per cent). Only 1 animal of the 5 treated for five seconds showed evidence of inhibition of mitosis. The number of mitotic figures in the corneal epithelium of the irradiated eyes of the other 4 rats did not differ significantly from normal.

In the studies of the effect of grenz rays on regeneration, standard thermal burns were inflicted on both eyes twelve to fifteen hours before autopsy. Since the burns of this severity and size were known to become covered with epithelium in approximately fourteen hours, any delay in this process caused by the irradiation would yield partially covered burns by the fifteen hour stage. On the other hand, if the healing process were stimulated, the healing of the irradiated corneas would be advanced at the twelve hour stage. All the comparisons necessary would be

<sup>9</sup> Kaufmann, B., Gay, H., and Hollaender, A. Distribution of Mitoses in the Corneal Epithelium of the Rabbit and the Rat, *Anat Rec* 90:161-178, 1944

made between the equally burned irradiated and control eyes of the same animal. The right eyes of 11 rats were irradiated one hour before the corneal burns were made and autopsied fifteen hours later. It was found that the epithelium had completely covered the denuded corneal stroma in both the irradiated and the control eye in all but 2 animals. Epithelization was not quite complete in 1 control and 1 irradiated eye in this group. Since irradiation and burning were done almost simultaneously, it appeared that the initial reaction of the tissues to the irradiation might obscure the more fundamental effects. Accordingly, another group, of 4 animals, was given two irradiations three days apart, and the corneal burns were made three days after the last irradiation. The animals were autopsied fifteen hours after the burn had been made. In this series any tissue reactions which immediately follow irradiation would have subsided. Epithelization was complete in all eyes, the control as well as the irradiated. Standard burns were made on a

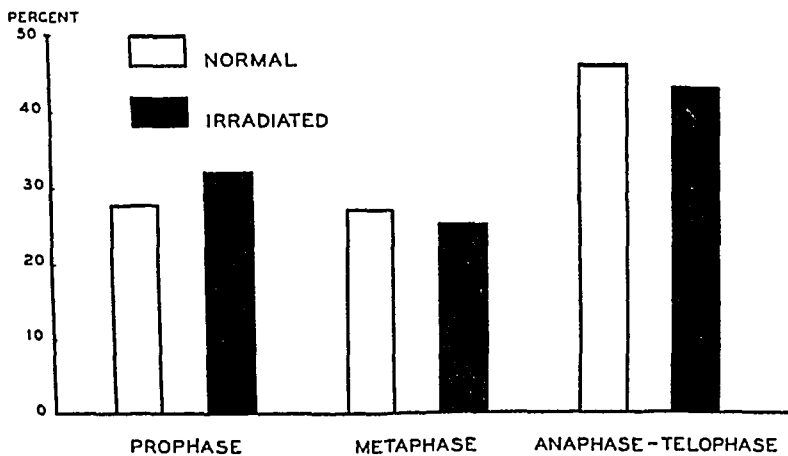


Fig 2—Proportions of phases of mitosis in the irradiated and in the control rat cornea

third group, of 5 animals, seventeen hours after a single irradiation, and autopsies were performed twelve hours after the burns had been made. At this stage epithelization is not quite complete in the normal eyes. In this series, also, grenz rays did not affect cell migration. In 2 rats the migrations of the epithelial cells were equal in the control and the irradiated cornea, and in 2 others the migration was less advanced in the irradiated eye. In the fifth animal epithelization of the control burn was slightly delayed as compared with that of the irradiated burn.

It will be noted that all the experiments on the effect of irradiation on regeneration were carried out during the postirradiation period, in which mitosis would still be inhibited. Counts of mitotic figures showed (fig 1) that the irradiation markedly inhibited cell division in the regenerating epithelium, although it did not inhibit the ability of the cells to move in over the denuded area. The degree of inhibition of mitosis

was almost exactly the same as that produced in intact epithelium. In view of this observation, it was thought advisable to study the rate of epithelization of burns in eyes which had been irradiated sufficiently in advance so that the depressing phase of the irradiation had been passed. Eight days after irradiation mitotic figures were uniformly more frequent in the treated than in the untreated cornea, in the experiments on intact eyes, therefore, this stage was selected. Both corneas of 6 rats were burned twelve hours before autopsy, and eight days after a single exposure of the right eye to grenz rays. In each case epithelization was greatly delayed in the irradiated eye. The size of the unhealed portion of the burns of the control eyes was normal for the twelve hour stage. The area of the unhealed portion of the burns of the irradiated corneas was much greater than that of the control burns. The number of mitotic figures was not depressed in 4 of the 6 animals, but a significant decrease in their number was noted in 2, namely — 41 and — 66 per cent respectively. The decrease in these 2 animals was responsible for the indicated depression of mitosis shown for this group in figure 1. This depression is probably to be explained by the fact that the area of epithelium on which the counts were based was so much less in these eyes, owing to the large unhealed area of the burn. These results led us to repeat the experiment on 7 additional animals, with similar results. The burns of the eyes irradiated eight days earlier healed more slowly than did similar injuries of the control eye. Twelve hours after the burn had been made the unhealed portion of the burns of the eyes irradiated eight days earlier was 152 per cent larger than that of the control burns. This inhibitory effect was consistent, for it occurred in 12 of the 13 animals studied. The healing of corneal burns of 5 other rats which had received grenz radiation to one eye ten days earlier was also studied. In this group the average unhealed area of the burn was greater in the irradiated eyes, but the inhibitory effect was apparently wearing off, for 3 burns healed normally.

#### COMMENT

The grenz rays share, in common with the regular roentgen and the ultraviolet rays, the property of inhibiting cell division<sup>10</sup>. Although they are generally regarded as harmless to the eye, owing to their inability to

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10 (a) Carlson, J. G., and Hollaender, A. Immediate Effects of Low Doses of Ultraviolet Radiation of Wavelength 2537 Å on Mitosis in the Grasshopper Neuroblast, *J. Cell & Comp. Physiol.* **23** 157-169, 1944. (b) Glucksmann, A., Tansley, K., and Wilson, C. W. The Effect of Variations in the Dose-Rate of Gamma Radiation on Cell Degeneration in the Frog Tadpole, *Brit. J. Radiol.* **18** 158-164, 1945. (c) Buschke, W., Friedenwald, J. S., and Moses, S. G. Effects of Ultraviolet Irradiation on Corneal Epithelium. Mitosis, Nuclear Fragmentation, Post-Traumatic Cell Movements, Loss of Tissue Cohesion, *J. Cell & Comp. Physiol.* **26** 147-164, 1946.

penetrate deeply into tissues, it is clear that the reproductive capacity of the irradiated superficial cells is greatly impaired for a relatively long time. It is important to note that the single dose used in these experiments was not excessive, but within the range given for therapeutic purposes.

The long, five day, inhibition caused by a single exposure to the rays was followed by a very short period in which mitotic figures were more frequent in the treated eye. This increase in mitosis, although consistent, was not much more than might be accounted for by normal variations. That the increase was certainly not great enough to make up for the five day deficit in mitosis is obvious on reference to figure 1. If the cell population remained constant during this period, the rate at which the cells died and were lost must also have greatly decreased.

From a biologic point of view, a most interesting condition is apparent. The two processes involved in healing, mitosis and cell migration, are not equally affected. The burns studied healed, as nearly as could be determined, at the normal rate while under the influence of an agent which reduced mitosis nearly 100 per cent. Similar, although not as striking, evidence of the separateness of these two phases was noted earlier in experiments with the effect of anesthetics on wound healing.<sup>11</sup> Buschke, Friedenwald and Moses<sup>10c</sup> also noted that ultraviolet radiation in amounts which inhibited mitosis did not deter post-traumatic cellular movements. There is no evidence that grenz rays inhibit processes necessary to protoplasmic movement involved in cell division, for no inhibition of mitotic activity was noted in those cells which had entered the active phases of this process, nor was cell migration following injury inhibited shortly after an irradiation.

There was no indication of a beneficial effect of grenz rays on either of the healing processes studied. Cell migration was at best not affected, whereas mitosis was definitely inhibited for several days after exposure to grenz rays. The experiments of Buschke, Friedenwald and Moses<sup>10c</sup> on the effect of ultraviolet radiation on mitosis showed that with weak doses mitosis was stimulated. A similar reaction was not noted with grenz rays when shorter exposures were given.

#### SUMMARY

- 1 Single exposure to grenz rays (410 r) greatly inhibited cell division in the corneal epithelium of the rat for approximately five days.
- 2 The period of inhibition was followed by a short interval in which a slight rise in the number of mitotic figures occurred. This increase in

11 Smelser, G. K., and Ozanics, V. Effect of Local Anesthetics on Cell Division and Migration Following Thermal Burns of the Cornea, *Arch. Ophth.* 34: 271-277 (Oct.) 1945.

mitosis was not sufficient to compensate for the five day deficit in cell division

3 Grenz rays did not affect cell division once the cells had entered the active stages of mitosis

4 Grenz rays had no effect on the rate of epithelization of thermal burns made within six days of the irradiation

5 Thermal burns made eight days after a single irradiation healed more slowly than normal in 12 of the 13 animals studied This inhibitory effect was conspicuously less by the tenth day after irradiation

630 West One Hundred and Sixty-Eighth Street

# INTRAMURAL VASCULAR SYSTEM (VASA VASORUM?) IN RETINAL VESSELS

ARNOLD LOEWENSTEIN, M D  
GLASGOW, SCOTLAND

**V**ESSELS within the wall of retinal vessels have not hitherto been recognized. In general, only the walls of vessels with a caliber greater than 1 mm are provided with vasa vasorum, the latter arising from adjacent small arteries and forming a dense capillary network in the adventitia. Even in larger arteries they do not penetrate farther than the external layers of the media. They are more abundant in the veins and here penetrate deeper, into the intima, and may even drain the lumen (Maximow and Bloom<sup>1</sup>).

In studying the retina in bulk after clearing in glycerin, I have, however, observed capillaries in the walls of diseased retinal vessels (Loewenstein,<sup>2</sup> 1946). I supposed at first that this capillary system represented unknown vasa vasorum, and therefore for years I hesitated to publish my results. It was not until I came across the work of Winternitz, Thomas and Le Compte,<sup>3</sup> entitled "Biology of Arteriosclerosis," that I understood my observations. These authors, using the clearing method in the study of pathologic tissue, were able to prove the existence of an intramural vascular system in the sclerosed aorta and in sclerosed coronary arteries. They stressed the importance of the presence of this rich vascular system in the intima within and around arteriosclerotic plaques. It is not less significant that this network was not observed in healthy vascular walls in young persons. Only in areas where these intramural vessels bridged a narrowed or occluded lumen might they pass through healthy tissue in the vascular walls to reach the affected parts. These authors observed the intramural vascular system within the diseased venous wall no less frequently than in the arterial wall, it being sometimes even highly developed.

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From the Tennent Institute, University of Glasgow, Prof W J B Riddell, Director.

1 Maximow, A A, and Bloom, W. A Textbook of Histology, ed 3, Philadelphia, W B Saunders Company, 1938

2 Loewenstein, A. Read at the meeting of the Oxford Ophthalmological Congress, July 5, 1946

3 Winternitz, M C, Thomas, R M, and Le Compte, P M. The Biology of Arteriosclerosis, Springfield, Ill, Charles C Thomas, Publisher, 1938

in veins. Enlightening to the ophthalmologist is a picture produced by these authors of the narrowed lumen of a renal artery with a rete mirabile forming a collateral channel system (page 77, fig 61<sup>3</sup>)

The significance of this collateral circulation may be very great where other routes are not available or insufficient in capacity, as for instance in the so-called end arteries of the coronary system

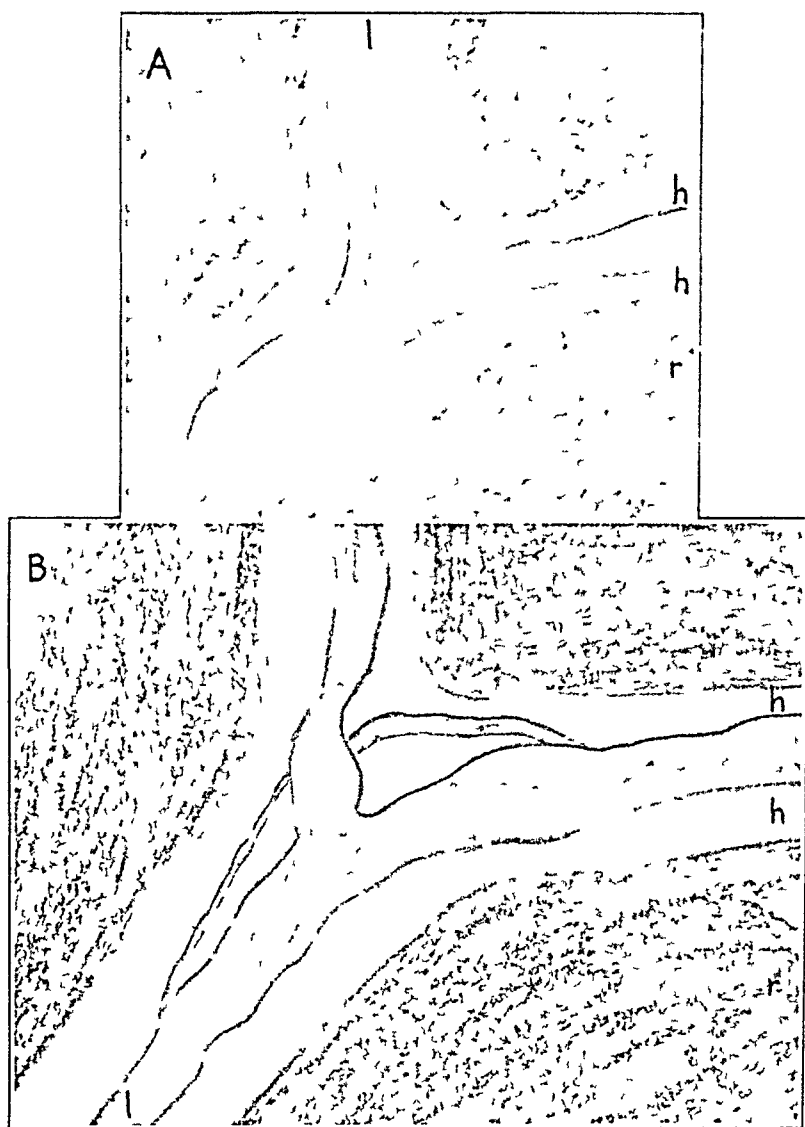


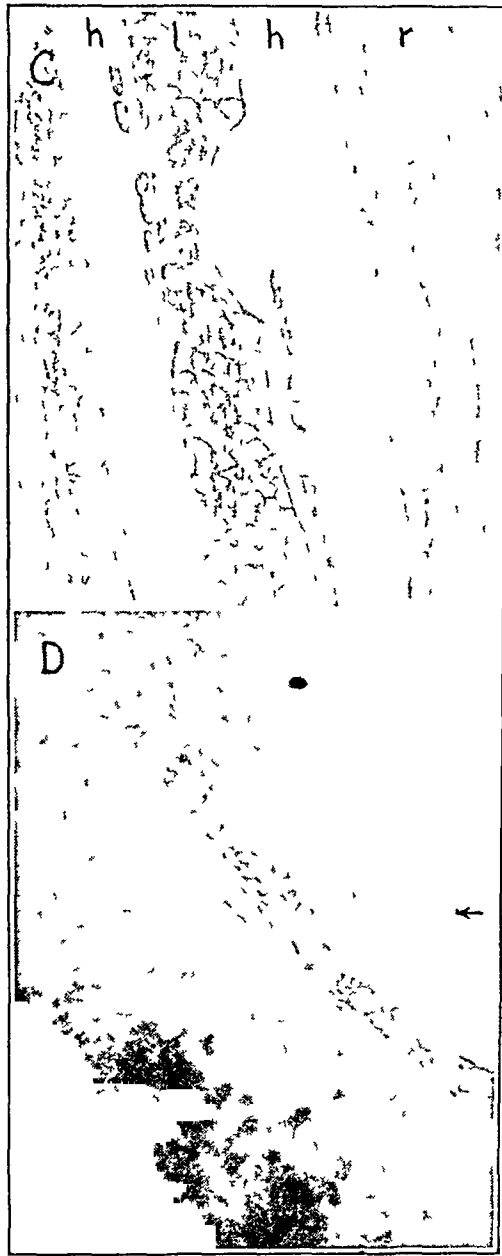
Fig 1—*A*, intramural capillary in the hyalin-thickened wall at a branching point. Retina in bulk,  $\times 250$

In this drawing, and in *B* and *C*, *l* indicates the lumen, *h*, the hyalinized wall of the vessel and *r*, retinal tissue

*B*, intramural capillary in the hyalin-thickened wall of a retinal vessel in a case of thrombosis of the central retinal vein. Retina in bulk, unstained,  $\times 250$

The ophthalmologist in reading this description is strongly reminded of changes in the fundus associated with thrombosis of the retinal branch

vessels, with arteriosclerotic and diabetic retinopathy and with so-called retinal periphlebitis. The similarity of this ramified intramural vascular system in diseased coronary arteries to a retinal or a preretinal rete mirabile is striking.



C, intramural capillaries in the sclerosed wall of a retinal vessel in a case of thrombosis of the central vein. Retina in bulk, unstained.

D, photograph of the retina in bulk, unstained ( $\times 107$ ) in a case of thrombosis of the central vein, showing an intramural capillary (arrow) remaining in focus.

Paterson <sup>4</sup> (1936) had described vascularization of coronary arteries in association with atherosclerosis. He did not observe these intramural vessels in normal arteries or in arteries with early nodular endarteritis.

<sup>4</sup> Paterson, J. C. Vascularization and Hemorrhage of Intima of Arteriosclerotic Coronary Arteries, Arch Path **22** 313 (Sept.) 1936.



They were particularly conspicuous in thrombosed coronary arteries. It is significant that he noted these intimal capillaries in close proximity to extravasated blood. This observation was confirmed and its importance indicated by Winternitz and his co-workers.<sup>5</sup> Paterson showed that these intimal capillaries arise not from the adventitial vasa vasorum but from the lumen of the partially occluded vessels. They may develop in response to nutritional requirements associated with the sclerosed plaque.

Paterson stated that Robertson,<sup>5</sup> in 1929, had already seen a discrete capillary system in the intima of the diseased ascending aorta. Leary<sup>6</sup> (1934) described proliferating intimal capillaries in 4 out of 21 cases

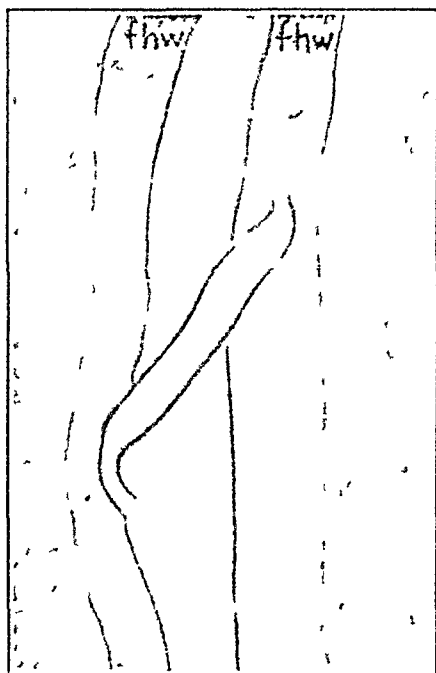


Fig 2—Retinal arteriosclerosis, with an empty intramural vessel running spirally. The fatty hyaline wall is indicated by *fhw*. Retina in bulk, stained with scarlet red,  $\times 112$ .

of coronary thrombosis. In 1 case a capillary showed an opening into the lumen.

#### INTRAMURAL VASCULARIZATION OF SCLEROSSED RETINAL VESSELS

My co-workers and I have observed single capillaries running within the hyalin-thickened wall of sclerosed retinal vessels. When they are filled with blood, these capillaries stand out sharply in the glycerin-cleared, unstained retina in bulk (fig 1 A, B and C). They are not easy

<sup>5</sup> Robertson, H. F. Vascularization of Thoracic Aorta, Arch Path 8 881 (Dec) 1929.

<sup>6</sup> Leary, T. Experimental Atherosclerosis in Rabbit Compared with Human (Coronary) Atherosclerosis, Arch Path 17 453 (April) 1934.

to distinguish when they are empty, as their walls are extremely thin. They rarely remain at one level. The sketches have been made, therefore, with constant change of focus, this variability of level being the reason that my attempts to get satisfactory photomicrographs have generally been unsatisfactory (fig 1). It is even more difficult with empty intramural vessels (fig 2). Sometimes I found a suitable intramural vessel running for a short distance at the same focus (fig 1 *D*). The contrast with the surrounding tissue was slight, and no distinction appeared on the ground glass of the microcamera. (Figure 2 was taken with the stereomicroscope, the capillary was not discovered with the microcamera.)

The majority of the intramural vessels run parallel with the lumen (fig 1 *A, B, C* and *D*). They are more frequent at points of bifurcation (fig 3). These intramural capillaries are observed in retina in bulk

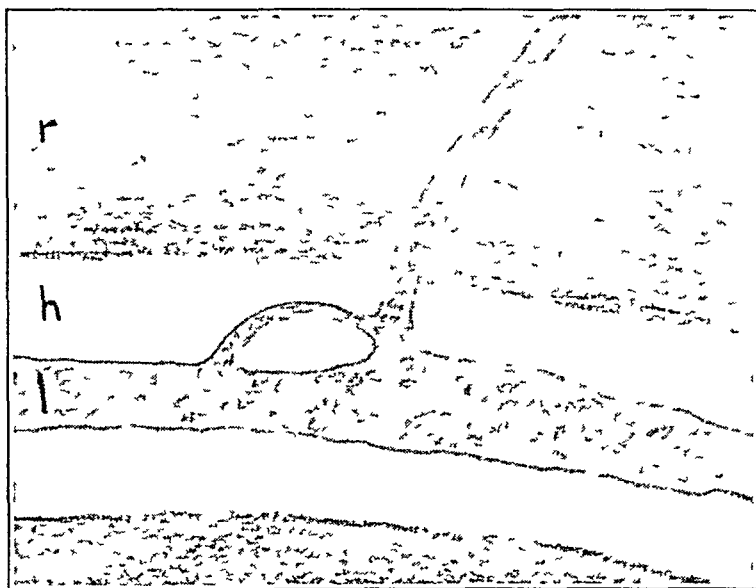


Fig 3—Hypertensive retinopathy with thrombosis of the central retinal vein, showing unusual branching. Retina in bulk, unstained,  $\times 240$

more easily if they do not run above or below the blood-filled lumen, but course tangentially, thus appearing in a deep, clear hyaline layer (fig 4), which provides sufficient contrast.

The opening of these capillaries into the lumen is difficult to demonstrate in bulk specimens but easy in serial sections (fig 5). This is also true of their branching, which was not seen with sufficient clarity in whole thickness specimens of the retina but could be shown easily in serial paraffin sections (fig 6).

We observed intramural vessels within the hyalin-thickened vascular wall running obliquely (fig 2), as well as vessels with a circular course, but the latter were less frequent than the vessels running longitudinally. In most cases the circular capillaries could be traced through half the circumference of the vessel (fig 7 *A, B* and *C*). We were unable to

distinguish origin and outlet in bulk specimens, but serial sections permitted reconstruction of the connection between the lumen and the adjacent retinal vessel. Here we could follow the opening into the lumen (fig 6), trace the division within the hyaline coat and even demonstrate reunion with the sister branch. This is proof of a modest

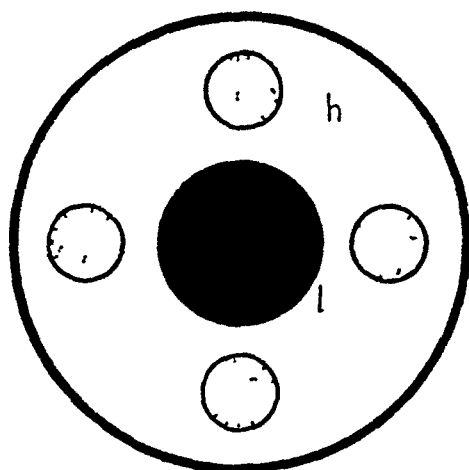


Fig 4—Schematic sketch of intramural vessels in a hyalinized wall, seen in the retina in bulk. The vessels are practically invisible when in front of or behind a filled lumen. They stand out sharply when seen tangentially. The hyaline wall is indicated by *h*; the blood-filled lumen, by *l*.



Fig 5—Intramural vessels with intramural sprouting. Hematoxylin and eosin stain,  $\times 300$ .

network. A spiral intramural course could be shown as well (fig 8). Interesting is the appearance of parallel vessels, the lumens of which are separated by one endothelial layer only (fig 9). We measured the length of this parallel course and found it to be from 100 to 160 microns.

This is a peculiar vascular arrangement, the significance of which is as yet obscure. It is never observed in normal retinal twigs. We noted frequently that the site of origin of the intramural vessels in the intima was surrounded by a group of endothelial nuclei. This observation may also have significance. The phenomenon is reminiscent of the sprouting of endothelial cells in growing embryonic capillaries. A cellular

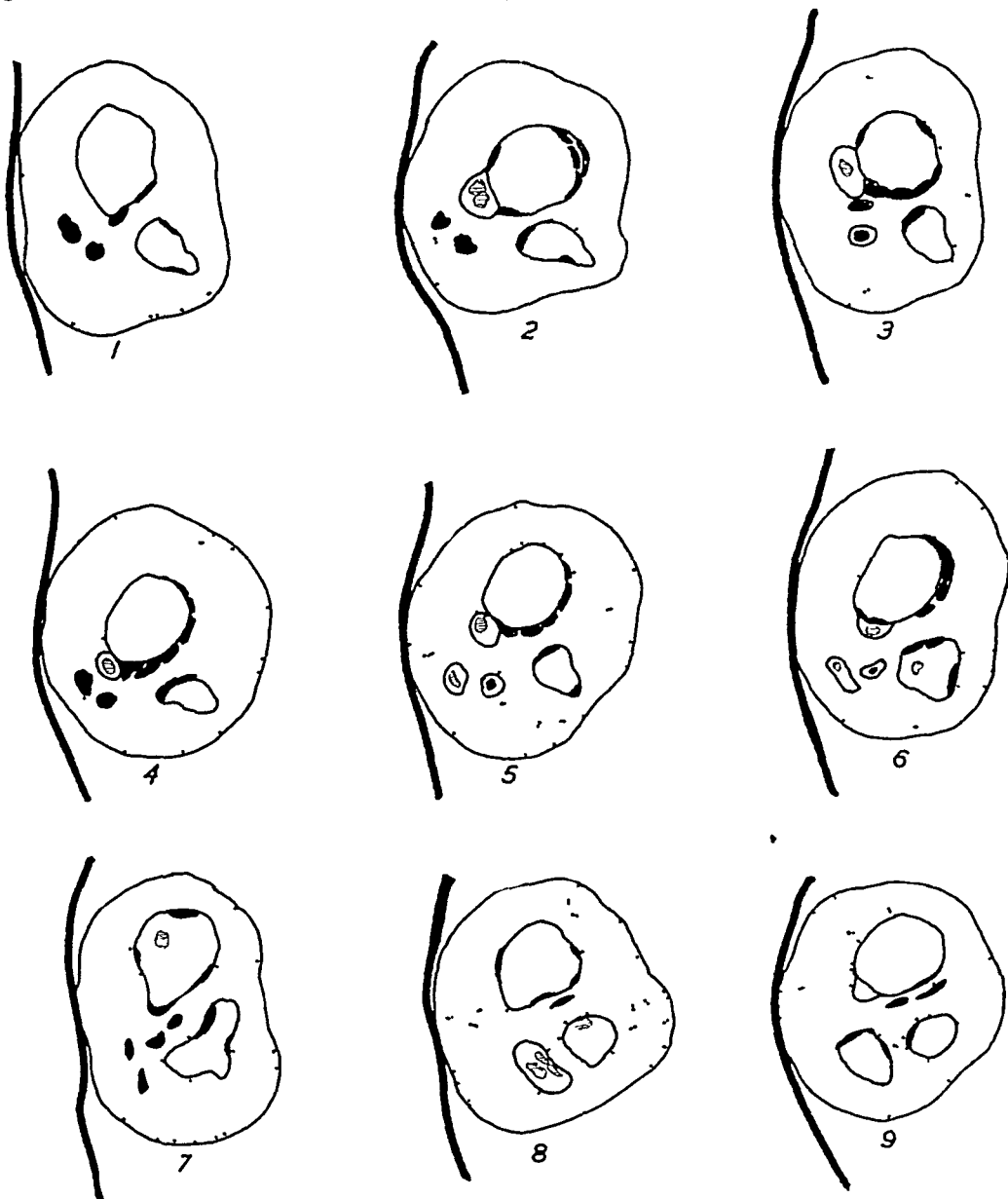


Fig 6—Hyalin-thickened retinal artery with intramural vessels. Note the intramural capillaries and their relation to endothelial nuclei. Some of the cross sections contain red blood cells. The capillaries unite and divide again, producing an intramural network. Hematoxylin and eosin stain,  $\times 160$

protrusion appears on the wall of the budding vessel, frequently in the form of a pointed cylinder. Maximow and Bloom<sup>7</sup> explained this embryonic budding on the basis of the increased demand of embryonic metabolism.

<sup>7</sup> Maximow and Bloom<sup>1</sup> p. 266

The intramural vessels are predominantly capillaries. Rarely one encounters an appearance like that in the section shown in figure 10, in which we observed a vessel running parallel to the main lumen, separated by an endothelial layer. But we were unable to find an endothelial lining in the smaller, blood-filled lumen of the unstained bulk specimen. Thus, we came to the conclusion that a kind of dissecting aneurysm was responsible for the production of this blood-filled canal, which was connected with the main lumen of a vascular bridge (fig 10). Serial

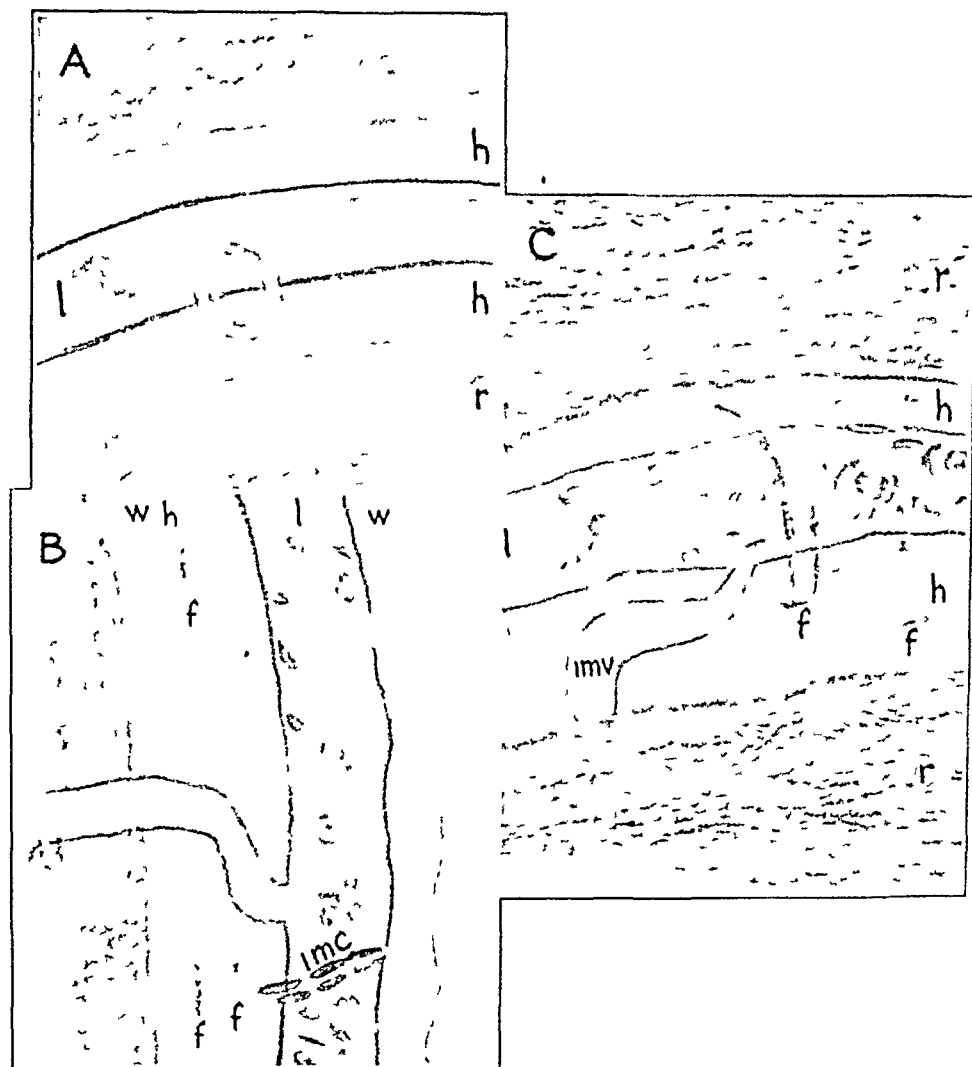


Fig 7—*A*, intramural capillary running in circular fashion within the hyaline wall. Fat droplets appear in the wall of the intramural vessel. Retina in bulk, scarlet red stain,  $\times 275$ .

Here, *h* indicates the hyaline wall, *l*, the lumen, and *r*, retinal tissue.

*B*, atheroma of retinal arteries, with asymmetric thickening of the wall (*w*) and ring-shaped intramural capillary (*imc*). Fibroblasts (*f*) contain fatty granules. Retina in bulk, scarlet red stain.

*C*, hypertensive retinopathy. Note the empty intramural capillary (*imv*) running across the hyaline vascular wall (*h*). The lumen is indicated by *l*, and the retinal tissue, by *r*. Retina in bulk, scarlet red stain,  $\times 275$ .

paraffin sections proved, however, that the "dissecting aneurysm" was a real intramural vessel. An endothelial lining was observed in the stained section.

The metabolism of a hyalinized vascular coat might be disturbed locally. The derivation of nourishment directly from the blood stream would meet with difficulties, which might be overcome by the budding of new capillaries from the endothelium. The growing intramural

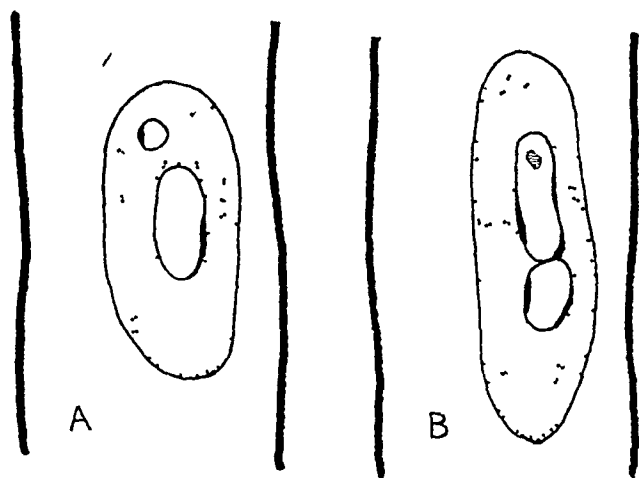


Fig 8—Hyalin-thickened vessel in a case of hypertensive retinopathy. One intramural vessel is followed in the series for 160 microns and runs in a spiral from A to B, where it unites with the main lumen. Hematoxylin and eosin stain,  $\times 175$ .

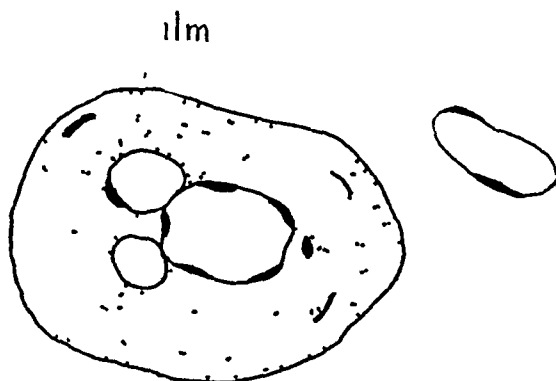


Fig 9—Hyalin-thickened retinal vessel. Two intramural vessels run close to the main lumen for 60 microns. Here, *ilm* indicates the internal limiting membrane, the drawing represents the entire retinal thickness. Hematoxylin and eosin stain,  $\times 190$ .

capillaries represent an emergency blood supply for a nutritionally menaced area.

We found newly formed intramural vessels in hyalinized arteriosclerotic vessels of the retina and concluded that the hyaline change is characteristically associated with this kind of vascular disease. Lately, however, we discovered a case of subendothelial fatty necrosis, a typical atheroma (fig 11), with a widespread intramural vascular sys-

tem Atheromatous changes within the retinal vessels are, therefore, not free from the formation of intramural vessels, as Winternitz and co-workers have shown in the coronary system

The extent of the intramural vessels is of course, far more limited than that of the extramural ones, which may produce a rich intraretinal

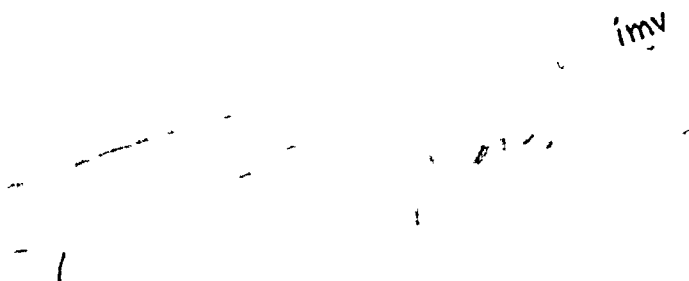


Fig 10—Hypertensive retinopathy, showing with large intramural vessel (*imv*) with branching toward the main lumen (*l*) Unstained retina in bulk

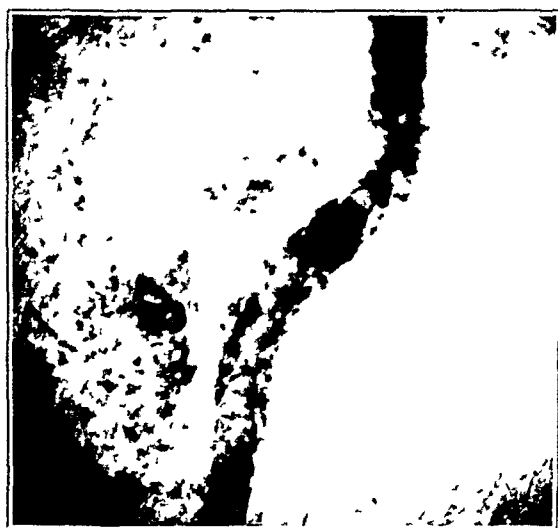


Fig 11—Atheromatous changes in a retinal artery consisting in fatty subendothelial necrosis, with many intramural vessels in its course Retina in bulk, scarlet red stain,  $\times 60$

and/or preretinal network This rete mirabile is encountered frequently in cases of diabetic retinopathy (Ballantyne and Loewenstein<sup>8</sup>) and

<sup>8</sup> Ballantyne, A J, and Loewenstein, A Pathology of Diabetic Retinopathy, Tr Ophth Soc U Kingdom (1943) 63 95, 1944

in cases of occlusion of the central vein, especially if the closing process proceeds slowly, with sufficient time for the production of an emergency blood supply. Such a rete is impressive in bulk specimens of the retina as the blood stain within this network penetrates the capillary wall (fig 12 *A*)

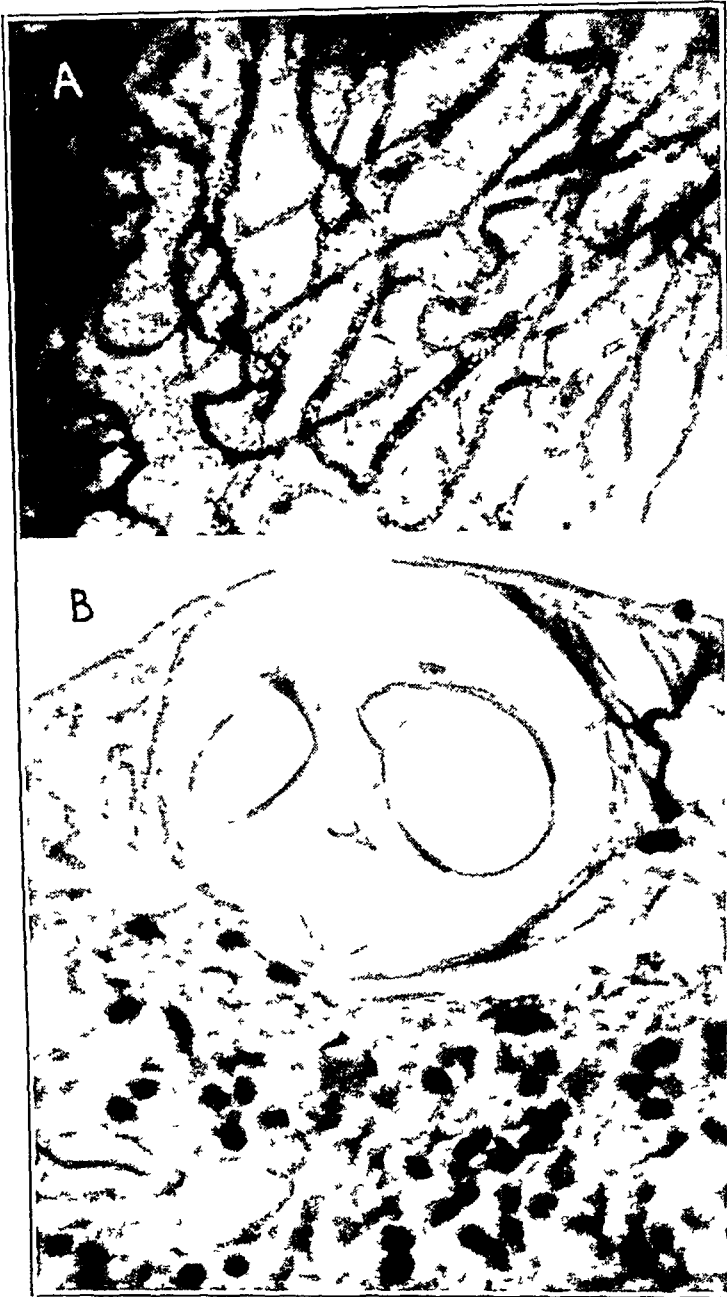


Fig 12—*A*, extramural new-formed capillaries in different layers of the retina in a case of thrombosis of the central vein. Retina in bulk, unstained,  $\times 150$

*B*, intramural vessels in a case of retinal arteriosclerosis. Paraffin embedding, hematoxylin and eosin stain,  $\times 30$

Knowing of the existence and appearance of intramural vessels in the arteriosclerotic vascular system of the retina (fig 12 *B*), I studied routine sections of paraffin-embedded eyes in cases of arteriosclerotic



vascular changes I encountered evidence of an intramural vascular system in many slides. Figure 13 is a section from an eye of a man aged 74 with arteriosclerosis which was excised after expulsive hemorrhage in the course of cataract extraction. Many small vessels within the hyalin-thickened wall of the central artery are to be seen in the sections (No study of serial sections was carried out in routine examinations.)

In a case of atheromatosis in an 11 year old boy with very high blood pressure and an aneurysm of the basal meningeal artery, we were unable to discover intramural vessels, in spite of far-reaching changes in the vascular coat. This absence of intramural capillaries in young persons may be significant.

In a case of thrombosis of the central vein with secondary glaucoma in a woman aged 41 there were a great mass of hemorrhages in all layers of the retina, a large number of microaneurysms and pronounced



Fig. 13—Intramural vessels (central retinal artery) in a case of expulsive hemorrhage occurring during cataract extraction, observed in routine sections. Hematoxylin and eosin stain,  $\times 280$ .

thickening of the coats of arteries and veins. Intramural capillaries were numerous in the retina in bulk. Routine pyroxylin-embedded sections (fig. 14) revealed a large number of intramural vessels, many of them being filled with blood. It was easy to differentiate an intramural hemorrhage (fig. 14 *B*) from an intramural capillary. In intramural hemorrhages no, or few, red blood corpuscles are deformed, most of them retaining their normal shape. In intramural capillaries (fig. *A* and *B*) seen in bulk specimens, however, the red blood corpuscles are greatly deformed, the cross diameter being about one-fourth the longitudinal one. This deformity according to Krogh,<sup>9</sup> is due to the active constriction of

<sup>9</sup> Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1922.

the capillary Hemorrhages from these capillaries were observed by Winternitz and co-workers,<sup>3</sup> who stressed the pathognomonic importance of the condition Paterson noted hemorrhages in the intima of coronary arteries associated with the intimal capillaries He concluded that the primary process was endarteritic, and then vascularization of

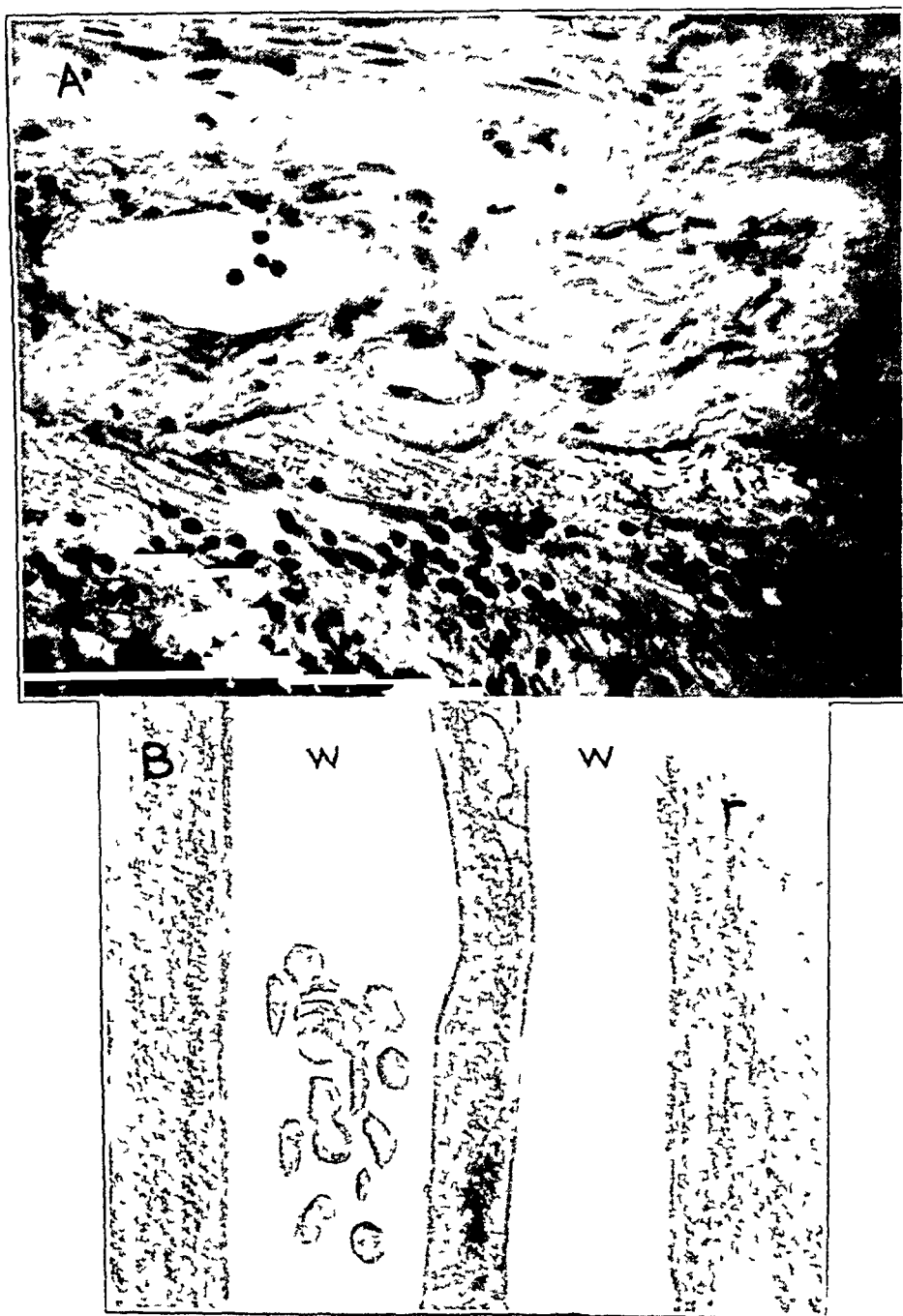


Fig 14—A, hyalin-thickened vascular wall with many intramural capillaries in a case of thrombosis of the central retinal vein The vessels had been observed before in clear, unstained specimens of retina in bulk Paraffin-embedded section, hematoxylin and eosin stain,  $\times 300$

B, hypertensive retinopathy, showing hyalin-thickened arterial wall, with hemorrhage within the tissue of the wall There is no deformation of the red blood corpuscles Retina in bulk, unstained  $\times 675$  In this drawing *r* is the retinal tissue, and *w*, the thickened vascular wall

the intima occurred, followed by softening of the surrounding stroma, until, finally, the capillary ruptured. We observed capillary hemorrhages in a case of combined hypertensive and diabetic retinopathy (fig 15). They were frequent in 2 cases of vasculitis retinac.

In flat, unstained retinal specimens (fig 16) fine channels ran parallel to the blood-filled central lumen. Some regular capillaries were conspicuous and sharply delineated. In other places a far more irregular system of capillary channels had replaced the main vessel (fig 17). In serial sections (fig 18) these vessels appeared to contain a multitude of endothelium-lined lumens, separated by a nucleated granular substance, in which lymphocytes, epithelioid cells and fibroblasts were visible. The presence of so many spaces produced a sieve-like appearance in cross section. Some of these vessels were filled with blood, some were empty. Serial sections showed that these vessels communicated

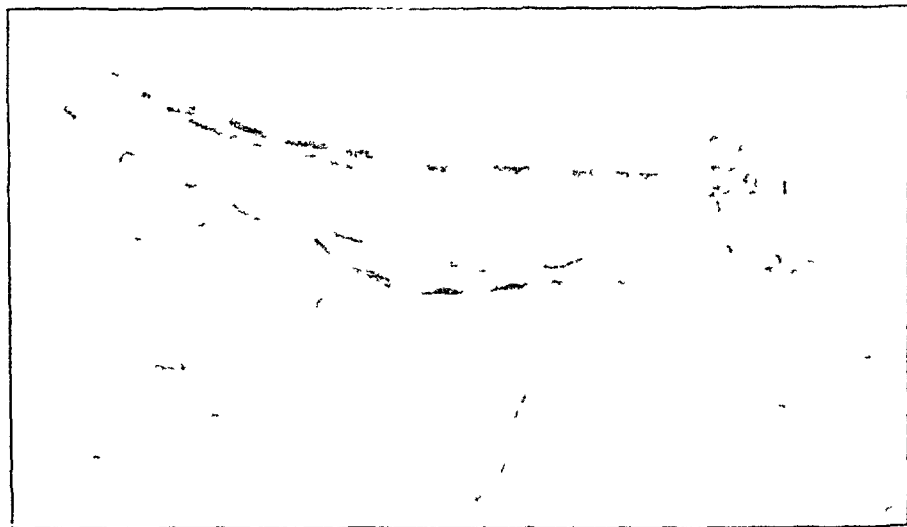


Fig 15—Two intramural vessels vanishing in a retinal hemorrhage in a case of hypertensive and diabetic retinopathy. Retina in bulk, unstained.  $\times 266$

freely with each other. At first we concluded that the process represented a primary thrombotic occlusion which had been canalized by the newly formed vessels. But study of slides in which the "thrombus" filled a part of the lumen only revealed that the intima covered the vascularized tissue without interruption. It is doubtful, therefore, whether this tissue is to be called a thrombus or whether it may better be considered a thickening of the wall due to a disease process.

Duguid<sup>10</sup> revived an old theory proposed by Rokitsansky (1852) concerning sclerotic thickening of the arterial wall. He expressed the belief that the subjacent endothelium disappears when a thrombus

10 Duguid, J. B. Thrombosis as Factor in Pathogenesis of Coronary Atherosclerosis, *J. Path. & Bact.* 58:207, 1946.

forms on the wall of an artery. A new lining of endothelial cells grows over the exposed surface of the thrombus. Thus, the thrombus becomes subendothelial in position and a part of the wall of the vessel.

This process may have taken place in the "thrombosed" retinal vessel in a case of vasculitis retinae which my associates and I reported (Loewenstein, Michaelson and Hill<sup>11</sup>). The mural disease may have caused the establishment of a thrombus, with vanishing endothelium at the site of adhesion and production of a new endothelial covering of the thrombus. The thrombus becomes incorporated in the wall of the vessel and is vascularized by newly growing capillaries from the lumen, as described in other instances of intramural vessels.

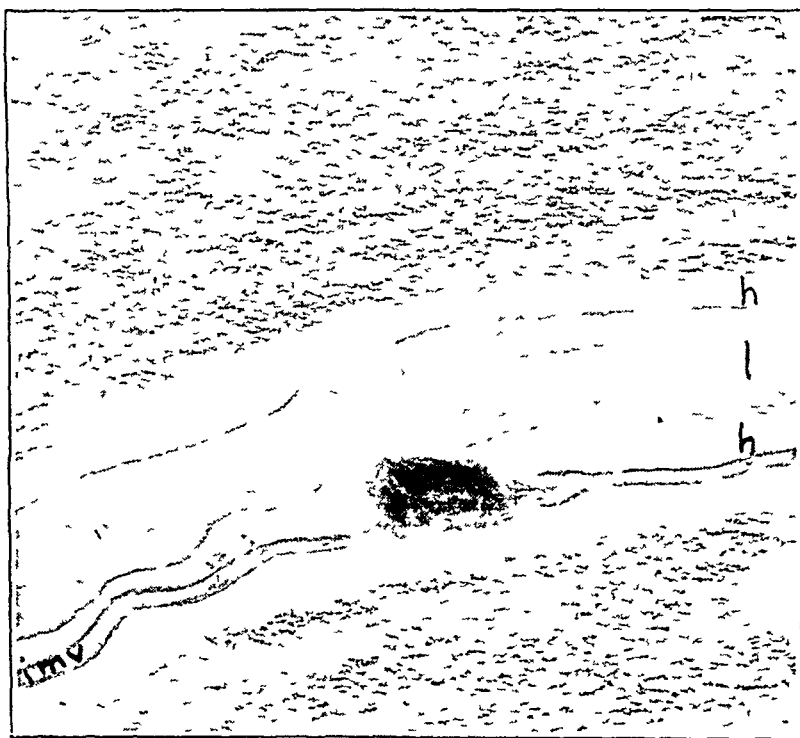


Fig 16—Intramural vessel with an intramural hemorrhage in a case of vasculitis retinae. Here, *l* indicates the lumen, *h*, the asymmetrically thickened hyaline wall, and *imv*, the intramural vessel. Retina in bulk, unstained,  $\times 300$ .

As already noted, the intramural vessels for the overwhelmingly greater part of their course remain within the hyalinized wall, whether they run parallel to the lumen, in circles or in spirals. Obviously, they serve the nutrition of a diseased tissue. Whereas the metabolism of the normal wall of the small retinal vessels is sufficiently maintained by the blood stream in the lumen, the diseased vessel wall, the hyalin-thickened coat especially, demands more nourishment. It may be that the changed consistency of the tissue acts as an impediment to the movement of fluid, filtration of which is rendered more difficult. It is likely that oxygen

<sup>11</sup> Loewenstein, A., Michaelson and Hill. Read at the meeting of the Ophthalmological Society of the United Kingdom May 30, 1946.

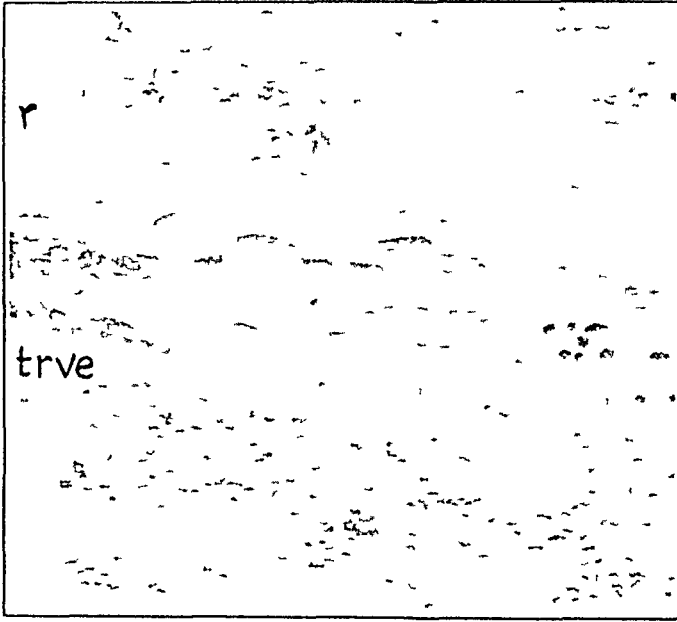


Fig 17—Thrombosed vessel with a multitude of new-formed, blood-filled channels (canalized thrombus?) in a case of vasculitis retinae (compare figure 18) Here, *r* indicates retinal tissue and *trve*, thrombotic and canalized retinal vessel. Retina in bulk, unstained.  $\times 257$



Fig 18—Vessel in the anterior part of the retina filled with a granulomatous tissue and perforated like a sieve with many thin-walled vessels. Paraffin embedding, hematoxylin and eosin stain,  $\times 300$

tension and lack of nutrition are responsible for the stimulation to formation of additional blood vessels. We believe that deficit metabolism of the hyaline tissue of the wall may supply the stimulus.

Under similar conditions, the metabolism of avascular corneal tissue is sufficient for all normal occasions. When the nutritional supply decreases, as in an inflammatory process, the damaged tissue calls for nutritional aid and gets it from the nearest vascularized area, i. e., the limbus, in the form of newly formed vessels.

Winternitz and co-workers<sup>7</sup> stressed the factor of the blood. If the lumen is narrowed, the nutritional capacity of the blood may become inadequate. They suggested that materials then exist in the blood which are potent stimuli for endothelial and capillary growth. The two factors may work together.

An interesting point is the tendency of the intramural capillaries to bleed. Paterson pointed out, correctly, that normally the intracapillary pressure is much less than the blood pressure in the aorta. The intramural vessels may rise from the lumen of the aorta under the aortic blood pressure, which is about twice the normal capillary pressure. These intramural capillaries consist of a simple endothelial layer, they may, therefore, easily rupture.

#### COMMENT AND CONCLUSION

Study of unstained retinal specimens cleared in glycerin has proved that capillaries are present in many sclerosed vascular walls. These intramural vessels may run parallel to the lumen or in circles or spirals. Examination of serial sections showed that the majority of the intramural vessels can be demonstrated to arise from the lumen, and that many of them may have a connection with another opening into the lumen. Others drain into extramural retinal vessels.

These vessels are different from normal twigs, as they leave the lumen closely attached for the most part to the endothelial lining of the lumen and remain for a considerable distance within the wall. Intramural ramification is the rule. Their wall consists of simple endothelium. Hemorrhage into the diseased wall from these intramural vessels is frequent, especially in cases of vasculitis retinae. I have not yet observed intramural retinal vessels in normal eyes, but they were discovered on reexamination of routine sections of eyes of patients with a sclerotic vascular system.

New formation of vessels in the diseased retina is a well known fact and frequently has been observed intraretinally and preretinally, on both ophthalmoscopic and anatomic examination. The existence of intramural newly formed retinal vessels has not hitherto been recognized. Their presence in vessels of such small caliber is surprising. They seem

to serve to improve a disturbed nutrition of the walls. New vessels in the coat of the diseased aorta and coronary arteries were described by Robertson<sup>7</sup> (1929), Leary<sup>8</sup> (1934) and Paterson<sup>9</sup> (1936) and were widely discussed by Winternitz-Thomas and Le Compte<sup>10</sup> (1938), who stressed the pathologic significance of these vasa vasorum in the intima of the diseased coronary arteries and aorta. The intramural vessels may serve to transport blood over an occluded or narrowed part of the lumen.

In general, such a process may perhaps be regarded as an attempt at healing of, or as compensation for a locally diseased part of the vascular wall.

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# STEREOSCOPE AS TRAINING INSTRUMENT

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## THE BREWSTER STEREOSCOPE AND MODIFICATIONS

THE FAMILIAR forms of the Brewster stereoscope consist of a pair of plus lenses decentered outward and mounted to permit convenient viewing of a pair of stereoscopic pictures through the lenses. These pictures have usually been set near the focal plane of the lenses to increase the illusion of distance by encouraging relaxation of accommodation and convergence.

Accommodation is relaxed and the lines of sight are parallel when two conditions are satisfied: when the targets are in the focal plane of the lenses, and when the centers of the targets for the two eyes and the optical centers of the viewing lenses are separated by the same distance. It is apparently the latter condition which accounts for the usual decentering of the lenses, for it permits the use of larger pictures.

When the stereoscope is used as a training device, it is customary to move the targets forward or backward to stimulate changes in accommodation. Demands on convergence have been changed by introducing different distances between the centers of the targets for the two eyes. An extension of this type of control is represented in the separate mounting of the pictures for the two eyes in holders which can be moved apart to provide any desired amount of separation between target centers.

A further development of these possibilities is represented by simultaneous change in the separation of the targets and in their distances from the lenses, as proposed by Dr. Samuel Renshaw, of Ohio State University. In the "stereo-disparator," which Dr. Renshaw has designed, the targets may be moved along paths which are parallel to the midline of the instrument, as in the usual stereoscopes, or they may be moved along paths inclined toward the midline. The relations of these target paths to the demands made on accommodation and convergence are the subject of the present study.

## ORTHOPTIC VIEWING WITH THE BREWSTER STEREOSCOPE

It has already been indicated that the accommodation and convergence of emmetropic, orthophoric observers are both relaxed, as for viewing objects at a distance, when stereoscopic targets are placed in the focal



plane of the lenses so that the distance between the centers of the targets is the same as the distance between the optical centers of the two lenses. Proof of this statement follows.

The image of a point will lie on a line from the object point through the optical center of the system, that is, in this case, from the center of the target,  $C$ , through the optical center,  $L$ , of the viewing lens of

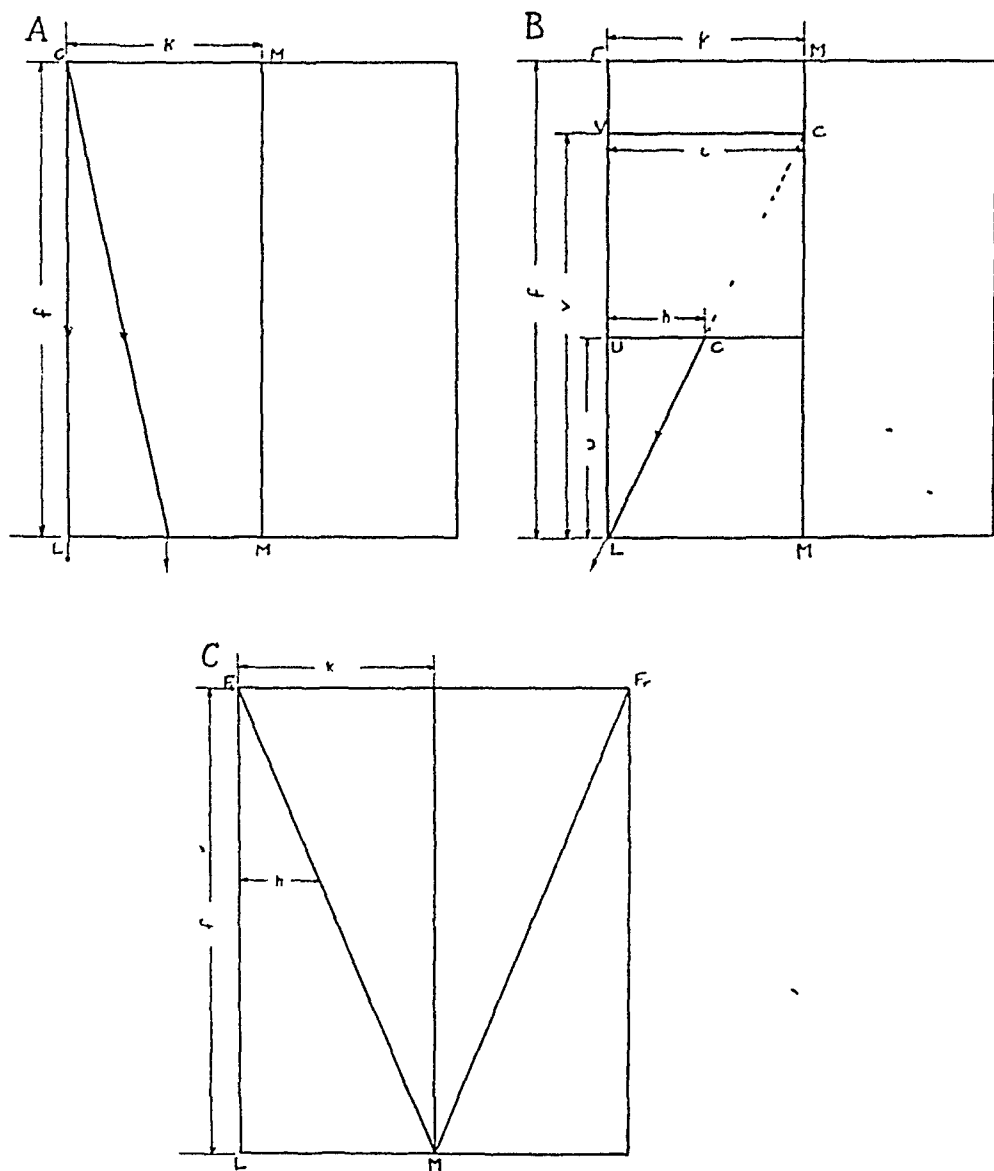


Fig 1—*A*, orthoptic viewing with the target in the focal plane. If the optical center of the viewing lens is at  $k$  centimeters from the midline of the instrument, the target center,  $C$ , must also be  $k$  centimeters out from the midline.

*B*, orthoptic viewing with accommodation in play. Light from the target center,  $C$ , at  $u$  meters from the plane of the lenses emerges as if originating at  $C'$ , on the median line at  $v$  meters from the plane of the lenses.

*C*, target paths for orthoptic views,  $F_1M$  and  $F_2M$ .

the stereoscope. When the target center and the center of the lens are at equal distances from the midline of the instrument and the target is in the focal plane, this line is parallel to the midline of the instrument, as shown in figure 1 *A*. Since all other rays from the same object point will emerge parallel to the ray thus represented when the target is in the focal plane of the lenses, all rays from the central fixation point will emerge parallel to the midline of the instrument, and any pair of eyes will assume the straight-ahead position in fixating the center of the picture binocularly, regardless of interpupillary distance. This is, of course, the orthophoric position for fixation of distant objects.

Precise description of the positions of the targets required for orthoptic viewing at nearer distances involves consideration of the elementary principles of optics. When stereoscopic pictures are viewed through the stereoscope, it is the virtual images of these targets which determine the direction of the lines of sight and the amount of accommodation called into play. If the central points of the two virtual images coincide on the median line of the system at some distance nearer than infinity, the demands on accommodation and convergence are related just as they normally are in viewing actual objects. Since the stereoscopic lenses are of the same power, the images will fall in the same plane when the two targets are in the same plane, and the accommodation,  $A$ , called into play will be inversely proportional to this distance, measured in meters.

Similarly, since the centers of the two lenses are at equal distances,  $k$ , from the midline, the centers of the two images will coincide on the midline only when the targets are equally displaced toward the midline from the optic axes of the two lenses. The exact amount of the displacement required is dependent on the distance of the targets from the plane of the lenses, as shown in the following discussion.

In figure 1 *B* let  $C$  be the center of the left target, which is at a distance of  $u$  meters from the plane of the lenses. Let  $v$  meters represent the distance of the image from the plane of the lenses. This distance can be calculated from the familiar lens formula

$$\frac{1}{v} = \frac{1}{u} + D$$

where  $D$  represents the dioptric power of the stereoscope lens.

Distances measured to the left of the lens when light is traveling from left to right are conventionally regarded as negative in sign, but difficulties can be avoided if one disregards this convention and substitutes negative signs in the lens formula for object-image distances, as follows

$$-1/v = -1/u + D \quad (1)$$

The center of the image,  $C'$ , can then be located by projecting the line  $LC$ , from the center of the viewing lens through the center of the

target, to its point of intersection with the image plane at  $v$  meters from the lens

In the similar triangles  $LCU$  and  $LC'V$ , thus formed, let  $h$  represent the displacement of the target center,  $C$ , from the optic axis, and let  $i$  represent the corresponding displacement of  $C'$ . Then,

$$h/i = u/v \quad (2)$$

The condition for orthoptic viewing is fulfilled whenever  $i = k$  for the two images, since  $k$  represents the distance from the center of the viewing lens to the midline of the stereoscope, and the virtual images will then coincide in the median plane. Substituting this value for  $i$  and replacing the value of  $1/v$  in equation (2) by its equivalent value from equation (1), one has

$$\begin{aligned} h/k &= u(1/u - D) \\ \text{and } h &= k(1 - uD) \end{aligned} \quad (3)$$

This formula gives the position of the target center,  $C$ , for orthoptic viewing when the target is at any distance,  $u$  meters, from the lens.

If the distance  $h$  is plotted for different values of  $u$ , it is found that all values of  $h$  fall on the straight line,  $F_1M$  of Figure 1.  $C = F_1$  represents the point at which the optic axis of the lens intercepts the focal plane. For this distance,

$$u = f = 1/D \quad \text{and, from (3), } h = 0$$

$M$  is the point on the midline in the plane of the lenses. For this point,  $u = 0$  and, consequently,  $h = k$ . A corresponding line,  $F_rM$ , represents the path for the target viewed by the right eye.

To summarize, demands on accommodation and convergence can be varied while conditions for orthoptic viewing are maintained if the targets are kept at equal distances from the lenses and follow, respectively, the paths  $F_1M$  and  $F_rM$ .

#### HETEROTROPIC VIEWING WITH THE BRLWSTER STEREOSCOPE

When the targets are separated more or less than the distance required for orthoptic viewing, prism effects are introduced which require that the eyes assume positions of relative divergence or excessive convergence for the distance of fixation. Maddox spoke of these positions as positions of artificial exotropia or esotropia.<sup>1</sup>

The amount of change from the orthoptic position measured in prism diopters, is dependent on the lateral displacement of the target from the position for orthoptic viewing and on the distance of the target from the lenses, as shown in figure 2.  $A$

If  $p$  represents the displacement of the target from the position for orthoptic viewing, the prism effect  $P$ , measured in prism diopters, will be proportional to the ratio  $p/u$  where  $p$  is measured in centimeters

<sup>1</sup> Maddox, E. E. The Bearing of Stereoscopes on the Relation Between Convergence and Accommodation, Brit J Ophth **11** 330-337, 1927

and  $u$ , the distance of the target from the lenses, is measured in meters. If the target is displaced outward from the line  $FM$ , the effect is that of base-in prism, and excess divergence is demanded, when the target is displaced nasally, base-out effect, with an excess demand on convergence, is introduced.

If one considers convergence as representing a positive function, and divergence as equivalent to negative convergence, it is convenient to regard  $p$  as positive when representing a nasalward displacement from  $FM$  and as negative when the displacement is outward (temporalward). The equation

$$P = p/u \quad (4)$$

will then give a positive value for  $P$  when the prism effect is base out, representing a stimulus to convergence, and will give a negative value for  $P$  when the effect is base in.

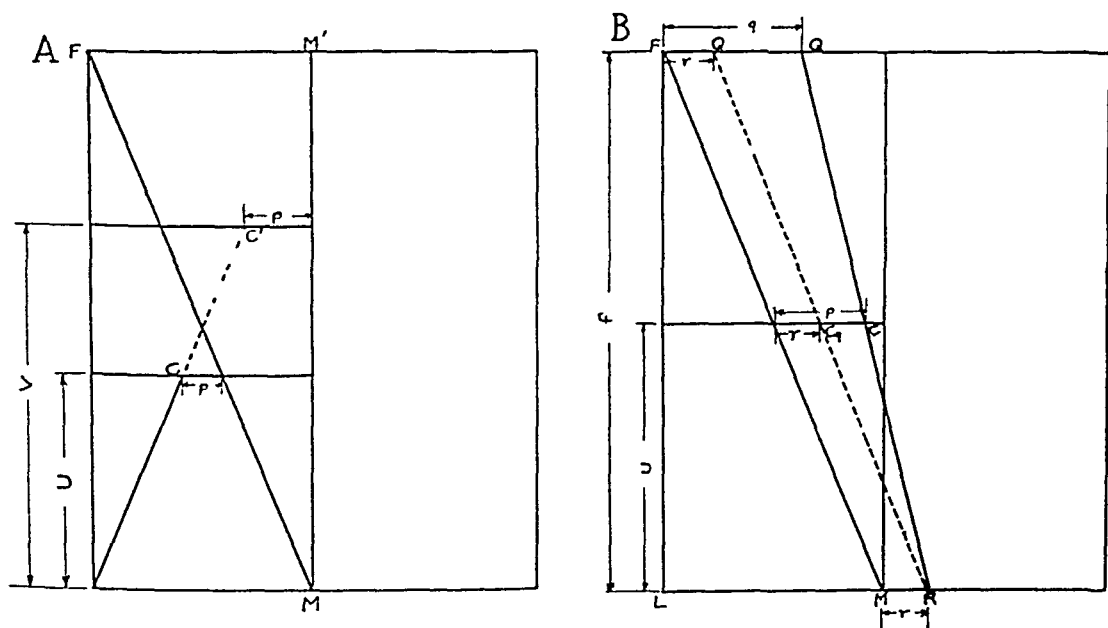


Fig 2—Heterotropic viewing (A) When the target center,  $C$ , is displaced  $p$  centimeters from the orthoptic path  $FM$ , the image  $C'$  is displaced  $p'$  centimeters from the median line (B) When the target follows the heterotropic path  $QR$ , the prism effect is determined by displacements from the orthoptic path of  $q$  in the focal plane,  $r$  in the plane of the lenses

As the targets are moved toward the observer, or away from him, along a straight line path, the prism effect will vary, depending on the inclination of the path with respect to  $FM$ , the path for orthoptic viewing, and on its distance from this path in any given plane. The two conditions are determined if these paths for heterotropic viewing are specified in terms of the distances from  $F$  and from  $M$  at which the path intercepts the focal plane of the lenses and the plane of the lenses themselves, respectively.

The prism effect introduced when the target follows a straight line path different from the orthoptic path can be determined as follows

In figure 2 *B*, *QR* represents such a path with displacement from the orthoptic path of *q* in the focal plane, *r* in the plane of the lenses. The target center, *C*, is displaced *p* centimeters. These quantities are positive when the displacement is toward the nasal side and negative when the displacement is toward the temporal side.

*Q'R* is drawn parallel to *FM*. In the triangles *C<sub>q</sub>RC* and *Q'RQ*

$$\frac{p-r}{q-r} = \frac{u}{f}$$

$$\text{and } p = r + (q-r) \frac{u}{f} \quad (5)$$

The prism effect, *P*, introduced when the target center is at *C*, is, from 4 and 5,

$$P = \frac{r}{u} + \frac{(q-r)}{f}$$

Substituting values

$$D = \frac{1}{f} \text{ and } A = \frac{1}{v} = \frac{1}{u} - D$$

$$P = rA + qD \quad (6)$$

Thus, for any point on any path, the prism effect of the target position can be specified in terms of the dioptric power of the viewing lenses, the direction of the path, as determined by its lateral displacements from the midline in two planes, and the demand on accommodation resulting from the distance between the target and the plane of the viewing lenses.

The general formula is correct for all cases. The only requirement is that the observer be emmetropic or wear his correction if the demand on accommodation is to be accurately represented by the value of *A*. Otherwise myopic subjects will be using less than the indicated amount of accommodation, while hypermetropic subjects will be exercising more than the amount indicated.

The interpupillary distance, which varies from one observer to another, is not a factor when the prism effect is thus considered always with reference to normal conditions of binocular fixation, here referred to as orthoptic viewing. This point of view also has the advantage of bringing the prism designation into harmony with measurements of heterophoria, convergence and divergence, since all these start with the position of orthophoria as the zero point. That is, deviations are regularly measured from the position in which the eyes are accommodated and converged for binocular fixation on a single target at any desired distance.

The simple formula thus resulting easily yields information about various target paths. For instance, the usual stereoscope provides for continuous movement of the targets only along lines parallel to the midline. When such a path starts at *F*, the focal point of the stereoscope lens, the conditions for orthoptic viewing are satisfied only when

accommodation is not in play For all nearer positions of the target, base-in prism effect is introduced, for

$$\begin{aligned} \text{when} \quad & i = -k \\ \text{and} \quad & q = 0 \\ \text{then} \quad & P = -kA \end{aligned}$$

This amount is doubled when the two eyes are considered Thus, if the stereoscope lenses are each decentered 5 cm from the midline, it appears that 30 D of relative divergence would be demanded with 3 D of accommodation for binocular fixation on targets following such paths

For parallel paths nearer the midline, the path will cross the path of orthoptic viewing, and the decreasing demand for excessive convergence will change to an increasing demand for divergence as the target is brought nearer the observer The point of crossing can be described as follows

$$\begin{aligned} P &= qD + iA \\ i &= -(k - q), \quad \text{for parallel paths} \\ P &= qD - (k - q)A \end{aligned} \quad (7)$$

The expression for  $P$  becomes 0 at the crossing point, for which

$$i = \frac{qD}{k - q}$$

For smaller values of  $A$ , excessive convergence is required for larger values, excess divergence is required

Further generalizations concerning target paths can be derived from considering cases in which  $q$  and  $i$  of the general formula are, in turn, equal to zero All paths for which  $i = 0$  converge toward a point on the midline in the plane of the lenses It follows that the prism effect for all such paths remains constant regardless of the demand on accommodation, as shown in the following equations

$$\begin{aligned} P &= qD + iA \\ i &= 0 \\ P &= qD \end{aligned} \quad (8)$$

for all paths converging to  $M$

In clinical terms, any path directed toward the midpoint of a line joining the optical centers of the two viewing lenses will provide a stimulus to a constant excess of convergence, positive or negative and zero in the special case of the orthoptic path The displacement required for any given effect is determined simply by solving the equation for  $q$ , that is, when

$$\begin{aligned} P &= qD \\ q &= P/D \end{aligned} \quad (9)$$

With the desired value for  $P$ , plus or minus depending on whether a base-out or a base-in effect is desired, and the known dioptric power of the stereoscope lenses substituted in this equation, the value of  $q$  is easily found and the target path can be arranged accordingly

For all paths for which  $q = 0$  (that is, which pass through the focal points of the lenses) the prism effect will vary directly with the demand on accommodation, for the equation becomes

$$\text{when } \begin{matrix} P = 1 + \\ q = 0 \end{matrix} \quad (10)$$

This means that for all positive values of  $i$ , as accommodation is stimulated, an increasing base-out prism effect is introduced. For negative values of  $i$ , the prism effect will be base in, increasing with accommodation, as in the case of parallel paths.

If, instead of changing the target paths, one decenters the targets with respect to any single path, the effect is equivalent to changing both  $i$  and  $q$  by the amount of decentration,  $i$  centimeters. Thus, the general equation becomes

$$P = (i + 1) A + (q + 1) D \quad (11)$$

It is often advantageous to decenter the targets, as Dr Renshaw has done with his size constancy series, because this makes it possible to bring corresponding points of the targets closer together. When it is desired to provide a strong, or even an adequate, stimulus to convergence with simultaneous strong stimulation of accommodation, the target must be decentered inward, and the consequent narrowing of the field must be accepted. Decentration of this sort is familiar with targets provided for use with ordinary stereoscopes. For instance, Sattler's *Stereoskopische Bilder für schielende Kinder* have been made only 5 cm in breadth, instead of the 9 cm which has become familiar through the use of the stereoscope as a simple viewing instrument.

*Clinical Applications of the Stereoscope*—Maddox<sup>1</sup> made clear the limitations of the stereoscope as a training instrument when the separation of corresponding points in the targets does not vary as the targets are carried toward or away from the viewing lenses, that is, when the targets follow paths parallel to the midline. Noting that this arrangement always means that positive convergence is stimulated as the demand on accommodation is decreased, and that negative convergence and positive accommodation are simultaneously stimulated as the target is brought toward the observer, Maddox recommended that in cases of divergence excess or convergence weakness the target be started from a plane near the observer and then be moved outward toward the focal plane of the lenses, whereas in cases of convergence excess and divergence weakness the target should be moved toward the observer. In either case the separation of the common elements of the two pictures is to be chosen so that the observer can fuse at the starting point, and so that he will be forced into his range of inadequate performance as the target is moved forward or backward. Krinsky<sup>2</sup> suggested that lenses

of different powers be inserted in the stereoscope as a means of increasing the ranges of movement forward and backward

Maddox noted that the orthophoric position for any distance of the target is independent of the interpupillary distance, and he calibrated a stereoscope so that the orthophoric setting was shown for any given separation between target centers. Thus, he established the points "beyond which convergence is greater than accommodation and within which convergence is less than accommodation," as he expressed it. The target centers must be nearer together than the centers of the lenses if this phrase is to be significant, as indicated in the preceding discussion of parallel paths. Even then, the functions of accommodation and convergence are always stimulated to respond in opposition to the normal pattern of association when targets are moved along parallel paths in exercises with the stereoscope.

This reversal of normal associations in the demands on accommodation and convergence may serve a purpose in training when it is desired to disrupt inefficient habits of accommodation-convergence association, as a step toward the substitution of more efficient associations. The usefulness of the ordinary stereoscope is limited if one is interested in encouraging positive development of efficient habits of association between these two functions.

The Renshaw modification changes this, making it possible to stimulate convergence and accommodation to respond according to the pattern required for normal conditions of viewing, or according to any other desired pattern which may seem indicated as a means of building up more adequate reserve powers in one function independently of the other. Also, emphasis may be put either on accommodation or on convergence, instead of being restricted to the type of accommodative stimulation which is associated with the desired type of convergence stimulation, as in stereoscopes of the type discussed by Maddox.

A further advantage of the Renshaw design, but one not peculiar to it, is the possibility of moving targets nearer together or farther apart without changing demands on accommodation, thus stimulating convergence quite independently of accommodation.

Thus, development of the Renshaw device makes it obvious that the full versatility of the Brewster stereoscope has not previously been utilized. As a training instrument, it was at first necessary always to stimulate accommodation and convergence simultaneously, but in an abnormal relationship, whenever considerable change in convergence was called for. Some changes could be brought about by requiring the observer to fixate successively different elements of the target design which had different degrees of disparity, but the range of movements

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2 Krinsky, E. *The Stereoscope in Theory and Practice*, also a New Precision Type Stereoscope, *Brit J Ophth* **21** 161-197, 1937



thus accomplished was very small. This limitation was partly overcome by the introduction of variable prisms, as in some of the English stereoscopes, or by providing for varying the separation of the two halves of the stereoscopic target. But the final step in this development was realized only when Renshaw proposed a means by which demands on accommodation and convergence could be varied, independently or simultaneously, and in any desired pattern of relationship. The foregoing discussion of the prism effects introduced by causing the targets to advance or recede along any selected paths, and the added effects introduced by decentration of the targets, should facilitate full utilization of this new and significant addition to the versatility of the stereoscope as a training instrument.

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# NEUROLOGIC SIGNIFICANCE OF LATERAL CONJUGATE DEVIATION OF THE EYES ON FORCED CLOSURE OF THE LIDS

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IT IS the purpose of the present communication to note and evaluate a diagnostic sign which, although described several decades ago (in 1913, almost simultaneously by Prezzolini<sup>1</sup> and Bárány<sup>2</sup>), has received scant attention<sup>3</sup> in the subsequent literature. The sign, a variant of Bell's phenomenon consists of a lateral conjugate deviation of the eyes on forced closure of the lids occurring in persons with intracranial disease.

After establishing the frequency of the sign in a series of persons with no known neurologic disease, observations were made on a group of approximately 200 persons with intracranial or labyrinthine lesions. Also noted were any evidence of paresis of conjugate gaze and any abnormality in the optokinetic response. Eliminated from the series were patients with probable bilateral lesions of the central nervous system or the labyrinth, patients observed only in coma or only after operation (except when the operation was a labyrinthectomy), patients showing insufficient evidence to localize the intracranial lesion and patients in whom the deviation was questionable, or consisted of wandering movements, first to one side and then to the other. There remained a group of 78 patients in whom the presence or absence of the sign might be expected to have reasonable significance.

Examination for the deviation of the eyes was carried out by forcibly separating the lids as the patient attempted to close the eyes (figure). A positive result was present when both eyes turned to one side consistently. Gross paresis of conjugate gaze to one side was said to be present when the eyes could not be fully moved to that side voluntarily or when a coarse jerking nystagmus developed on the

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1 Prezzolini, M. Deviazione coniugata dei bulbi oculari, associata alla chiusura delle palpebre, nell'emiplegia, *Bull d sc med*, Bologna **84**:285, 1913.

2 Bárány, R. Latente Deviation der Augen und Vorbeizeigen des Kopfes bei Hemiplegie und Epilepsie, *Munchen med Wchnschr* **16** 900, 1913.

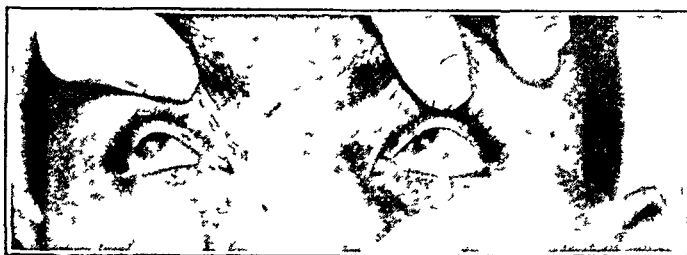
3 Bárány, R. Modern Labyrinthology, *Laryngoscope* **31** 401, 1921.

subject's looking to one side, with slow drifting of the eyes back toward the midline. The optokinetic response was tested by rotating in front of the patient a 12 inch (30 cm) drum having black figures on a white background. An abnormal, optokinetic response was said to be present when the nystagmus produced was much less to one side than to the other or when it was not elicited at all.

The lesions were localized chiefly by symptoms and/or by operation. Few of the patients were examined post mortem, and conclusions drawn from the series must be tempered by allowance for the fallibility of symptomatic and operative localization.

### RESULTS

*Control Series*—Of 156 persons with no known neurologic disease, lateral conjugate deviation of the eyes with closure of the lids was observed in only 3. Deviation of the eyes up or up and out occurred in 132, no deviation from the primary position was observed in 11,



Conjugate lateral deviation of the eyes on forced closure of the lids in a patient with a tuberculoma in the left occipitoparietal region. The only ocular motor disturbances were absence of the optokinetic response on rotating the drum to the patient's left and a spontaneous deviation of the eyes to the patient's right on attempted closure of the lids. The patient also had some hyperactivity of reflexes in the limbs, a positive Babinski sign and partial hemianopsia on the right.

convergence occurred in 5, downward deviation, in 3, and wandering movements in 2.

*Cerebral Lesions*—Of the 54 patients with presumed unilateral disease of the cerebrum, 34 showed a lateral conjugate deviation of the eyes to the side opposite the lesion, 5 showed a deviation to the same side as the lesion and 15 showed no deviation, with closure of the lids.

Of the 34 patients showing deviation of the eyes to the side opposite the lesion, localization of the lesion was considered reasonably certain in all but 8. Unilateral spasticity of the extremities or a positive Babinski sign on the side toward which the eyes deviated was present in 15 of the 24 patients whose visual fields were examined. A coarse nystagmus was present in 1 patient on looking toward the side of the lesion, and reluctance to look to that side, without any definite paresis, was noted in another. The other patients showed no evidence of paralysis.

of conjugate gaze Of the 34 patients showing deviation of the eyes to the side opposite the cerebral lesion, the optokinetic response was tested in 20 It was abnormal in 13 (defective response on rotation to the side of the lesion), normal in 7 and questionable in 1, and in 1 patient it was abnormal on one occasion but normal subsequently The cerebral lesion had been present in the majority of patients a minimum of several weeks The extremes of duration of the lesion were represented by a patient who was examined within twenty-four hours after the cerebral injury and by another who was examined three years after the injury In at least 2 patients the deviation of the eyes on closure of the lids persisted longer than any other neurologic sign Another patient whose eyes had been examined as part of a routine work-up for suspected hypertension less than twenty-four hours prior to the vascular accident, was found to have no deviation of his eyes, but examination one week after the accident revealed the presence of the deviation

The types of cerebral lesions represented in this series were as follows: vascular accident, 14 patients, tumors, 11 patients, injuries, 3 patients, tuberculoma, 1 patient, and undetermined type 5 patients The lesion involved predominantly the anterior part of the cerebrum in 6 patients, the middle portion in 7, the posterior part in 3 and the whole cerebrum or its efferent tracts in 18

Of the 5 patients showing deviation of the eyes to the side of the lesion, the localization of the lesion was reasonably certain in 4 Some degree of spasticity of the extremities was noted in 4, and a homonymous scotoma was present in 1 of the 3 patients on whom field studies were made Conjugate paresis of gaze was not observed in any of the patients There was no definite relation between its presence or absence and the optokinetic response In all patients of this group the lesion had been present for a minimum of several weeks

Of the 15 patients with presumed unilateral cerebral lesions who showed no deviation of the eyes, the localization was considered reasonably certain in 9 Some spasticity of the extremities was noted in 10, and homonymous scotomas (either positive or negative) were observed in 4 of the 12 patients on whom studies of the field were made Gross paresis of conjugate gaze was not observed in any of the patients There was no consistent relation to the presence of disturbances of the optokinetic response The case of a patient who had repeated convulsions, consisting simply of turning of the head and eyes and flexion of the arm on one side, was especially noteworthy, since the symptoms pointed to a circumscribed disturbance in the region of the frontal optomotor center and yet no deviation of the eyes with closure of the lids occurred between the convulsive seizures Another

patient of the group had convulsions in which the eyes turned to one side and yet no deviation of the eyes on closure of the lids occurred between the attacks

*Noncerebral Lesions*—Observations were similarly made on patients with lesions of the cerebellum and the brain stem. The lesions, however, were less definitely limited to one side of the midline and the results were inconclusive. Of 6 patients who were presumed to have unilateral cerebellar lesions, 3 showed deviation of the eyes to the side of the lesion on closure of the lids, and 3 to the opposite side. Of 10 patients with presumed unilateral lesions of the brain stem, 4 showed deviation of the eyes to the side of the lesion on closure of the lids, 3, deviation to the opposite side, and 3, no deviation. With unilateral lesions of the labyrinth, the results were also inconclusive, 4 patients showed deviation to the side opposite the lesion, 2, deviation to the side of the lesion, and 2, no deviation. Of incidental interest is the observation that a significantly large number of patients (about 25 per cent) with congenital nystagmus of the jerking type, in which the visual acuity is relatively good but the opticokinetic response is defective, showed conjugate lateral deviation of the eyes on forced closure of the lids.

#### COMMENT

In general, the results confirm the observations of Prezzolini and Barány in that unilateral cerebral lesions usually induce a conjugate deviation of the eyes to the side opposite the lesion when the lids are forcibly closed. However, no consistent deviation could be demonstrated with lesions of the cerebellum, brain stem or labyrinth.

The occurrence of the phenomenon does not depend on paralysis of conjugate gaze. It is often present in patients who show no paralysis of conjugate gaze (cerebral lesions) and may be absent in patients with gross limitation of conjugate gaze (lesions of the brain stem). Furthermore, the predominant direction of the deviation on closure of the lids (to the side opposite the lesion in cases of cerebral disease) is contrary to what one would expect if it were due to paralysis of conjugate gaze. The most likely explanation of this seeming paradox is to assume as Barany did, that, analogous to the condition in spastic hemiplegia there is increased tonus on the side on which, under appropriate conditions, it is manifested as palsy, and that when the fixation reflex is abolished by closure of the lids the eyes deviate in the direction of greater tonus. This condition may be called spasticity of the conjugate oculomotor mechanism and, like its counterpart in the limbs, is postulated to be the result of supranuclear lesions in the central nervous system.

There is adequate theoretic support for such a concept, since the innervation of the ocular muscles is similar to that of other voluntary

muscles Each half of the cerebrum represents the centers for conjugate gaze to the opposite side The eyes are held in symmetric position only so long as the innervations from the two halves of the brain are equal, and any asymmetry in the tonus, such as occurs with a supranuclear lesion, would be expected to result in a conjugate deviation of the eyes In the case of the eyes, this inequality in tonus becomes manifest as a deviation of the eyes when the fixation reflex is abolished by closure of the lids

This spasticity of the conjugate mechanism to one side may account for the curious occurrence that with cerebral lesions the nystagmus may be greater to the side of the lesion than to the opposite side, as would be expected on a paralytic basis It may also explain the reports of Guillain and Mollaret<sup>4</sup> and Klein and Stein,<sup>5</sup> in which patients with paralysis of voluntary conjugate gaze to one side were reported to have shown spontaneous turning of the eyes to the paralyzed side when the stimulus for fixation was removed

Although the foregoing explanation applies to the majority of observations on the patients with cerebral lesions here reported, one cannot overlook the fact that there were exceptions Some of these exceptions may have been due to limitations which were not, or could not be, controlled The fallibility of symptomatic and operative localization has already been noted There is also a personal source of error in making the initial records and transcriptions Because of this discrepancy, deviation of the eyes with closure of the lids can have only correlative significance at present When occurring with cerebral lesions, it suggests the side of the lesion but is not a wholly reliable sign

#### SUMMARY AND CONCLUSIONS

Lateral conjugate deviation of the eyes with closure of the lids is relatively infrequent in persons with no known neurologic disease Of the present series of 156 persons, it occurred in only 3

With unilateral cerebral disease, a lateral conjugate deviation of the eyes with closure of the lids does occur in a significantly large percentage of patients, e g, it was present in more than one-half the present series The deviation is characteristically to the side opposite the lesion (that is, to the side of the hemiplegia and hemianopsia) It occurs with lesions in the anterior or the posterior part of the hemi-

4 Guillain, G, and Mollaret, P Etude clinique sur un phénomène non décrit dans la paralysie des mouvements de latéralité des yeux la disparition de cette paralysie par l'occlusion palpébrale, *Rev neurol* **2** 74, 1931

5 Klein, R, and Stein, R Ueber eigenartige Bewegungsautomatismen der Augen und ihren Einfluss auf Kopf und Körper bei einem Fall von fast totaler Blicklahmung, *Zentralbl f d ges Neurol u Psychiat* **153** 242, 1935

sphere. However, with presumably unilateral lesions of the cerebellum, brain stem or labyrinth, the deviation of the eyes with closure of the lids was not significantly more frequent to one side than to the other.

The predominant direction of deviation of the eyes on closure of the lids in cases of cerebral lesions is opposite that in which paralysis of conjugate gaze occurs and is assumed to be due to an increased tonus of the conjugate mechanism, analogous to spasticity of other muscles under voluntary control.

As a cognate sign of unilateral cerebral disease, deviation of the eyes on closure of the lids supplements, but does not replace, other signs. It may be present or absent when there is, or is not, gross paresis of conjugate gaze. Similarly, it may be present or absent with or without disturbances of the optokinetic response, and with or without hemiplegic or hemianopic disturbances.

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# CHEMOSURGICAL TREATMENT OF CANCER OF THE EYELID

## A Microscopically Controlled Method of Excision

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**S**ELECTIVE destruction of accessible forms of cancer is attained, in effect, with the microscopic control of excision afforded by the chemosurgical technic. The development of the chemosurgical method in the laboratory<sup>1</sup> and in the clinic<sup>2</sup> has been described, as has the use of the method in the treatment of cancer in specific sites, such as the lip,<sup>3</sup> nose<sup>4</sup> and ear<sup>5</sup>. The present article concerns the chemosurgical technic as applied to the treatment of cancer of the eyelid, and it presents the end results in 99 cases at the three year period and in 73 cases at the five year period.

### TECHNIC

In the chemosurgical treatment of cancer of the eyelid, as in the treatment of cancer in other sites, the microscopic control is accomplished by means of a process consisting of the following steps: (1) in situ chemical fixation of the tissues suspected of being cancerous by means of a zinc chloride paste, (2) excision of a layer of the fixed tissue, (3) location of the cancerous areas by systematic microscopic examination of the excised tissues, (4) further chemical treatment of the areas demonstrated to be cancerous, and (5) repetition of the process until the cancer, including all its irregular extensions, has been entirely excised.

In order to illustrate the way in which the chemosurgical technic is used in the treatment of cancer of the eyelid, there will be described the chemosurgical excision of a cancer of the inner canthus (fig 1A). For two years the patient

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From the Department of Surgery, Dr. E. R. Schmidt, chief, State of Wisconsin General Hospital, and the McArdle Memorial Laboratory for Cancer Research, University of Wisconsin Medical School.

1 Mohs, F. E., and Guyer, M. F. Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, *Cancer Research* **1**: 49 (Jan.) 1941.

2 Mohs, F. E. Chemosurgery: A Microscopically Controlled Method of Cancer Excision, *Arch. Surg.* **42**: 279 (Feb.) 1941.

3 Mohs, F. E. Chemosurgical Treatment of Cancer of the Lip: A Microscopically Controlled Method of Excision, *Arch. Surg.* **48**: 478 (June) 1944.

4 Mohs, F. E. Chemosurgical Treatment of Cancer of the Nose: A Microscopically Controlled Method, *Arch. Surg.* **53**: 327 (Sept.) 1946.

5 Mohs, F. E. Chemosurgical Treatment of Cancer of the Ear: A Microscopically Controlled Method of Excision, *Surgery* **21**: 605 (May) 1947.



had been aware of a crusted ulcer near the inner canthus. The lesion was treated with radium on three occasions, the last being one year prior to his entrance to the chemosurgery clinic, but the growth had continued to spread.

The lesion, which measured 10 by 15 mm, consisted of an area of induration, in the center of which there was a crusted ulcer. The limits of the induration were indefinite, apparently because of the invasive nature of the neoplasm and because of the scarring from previous treatment.

After preparation with 0.03 Gm of codeine sulfate and 0.65 Gm of acetylsalicylic acid, the skin overlying the indurated area was given an application of dichloroacetic acid. This keratolytic chemical turned the skin white as it penetrated through the keratin layer, its function was to render the skin permeable to the fixative. The first application of the zinc chloride fixative<sup>6</sup> was made to a depth of 1 mm. The fixative was covered with a thin cotton dressing, which, in turn, was covered with an overlapping cotton dressing, spread with petrolatum to form a moisture-tight closure. Narrow strips of adhesive tape were accurately applied to hold the

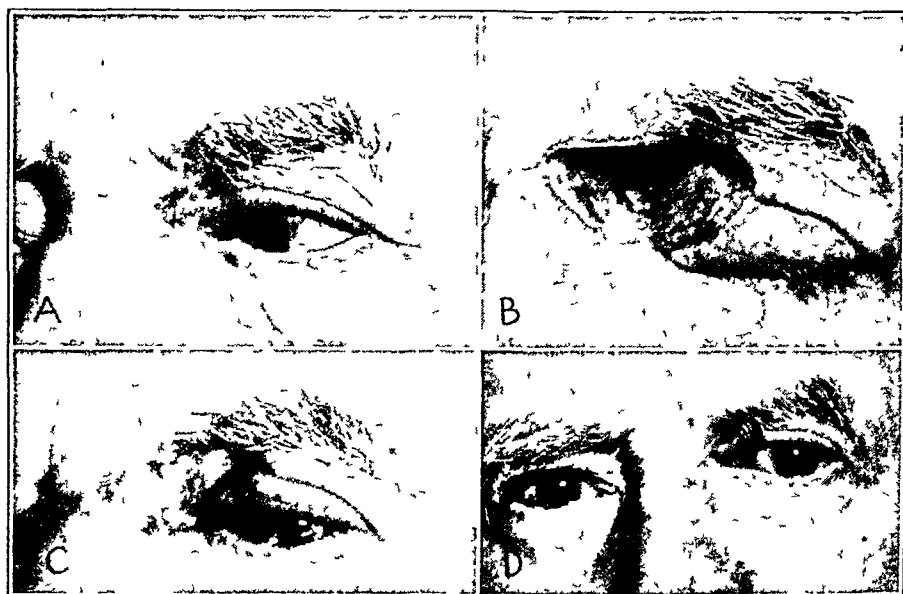


Fig 1—*A*, basal cell carcinoma of group B (average diameter, 1 to 2 cm). Starting at the inner canthus, the lesion had recurred after three radium treatments. *B*, lesion after chemosurgical excision of the cancer in four microscopically controlled stages (see fig 2). The final layer of fixed tissue is adherent. *C*, granulation tissue after separation of the final layer of fixed tissue after seven days. *D*, healed lesion after four months.

dressing firmly in place. The analgesics previously mentioned were ordered to be given as often as every three hours, as needed.

On the next day a layer of fixed tissue 3 mm thick was excised with a scalpel. There was no pain or bleeding from this operation because the incisions were made through killed and fixed tissue. A frozen section, cut vertically, revealed that the area was full of highly invasive basal cell carcinoma, although none could be distinguished by gross examination of the exposed surface, partly because of the

<sup>6</sup> This fixative paste contains 40 Gm of stibnite (80 mesh sieve), 10 Gm of powdered sanguinaria N F and 34.5 cc of a saturated solution of zinc chloride U S P.

scarring from the previous radium treatment and partly because the cancer grew as slender strands interspersed between the connective tissue fibers. The fixative was reapplied to the lesion to a depth of about 0.5 mm.

The next day a 2 mm layer of fixed tissue was excised. Since gross inspection of the surface gave no indication of the presence of cancer, the entire area was subjected to microscopic examination. This was done by means of a process consisting of the following steps: (1) division of the excised layer into five specimens, the locations of which were mapped on the lesion (with merbromin N F) and on a pad of paper (fig 2 A), (2) cutting of sections on the freezing microtome through the under surface of each specimen, and (3) examination of the specimens under the microscope and marking of the areas of cancer on the paper map with red pencil (stippled on the accompanying diagrams).

As shown on the diagram (fig 2 A), there were three areas of cancer. Application of the fixative was limited to these areas.

On the next day another layer was excised from the areas. It was divided into nine specimens (fig 2 B). Further treatment was limited to the one cancerous area, which was located in the cleft between the tarsal plate and the orbital part of the orbicularis oculi muscle. The next day no cancer was observed in the last area (fig 2 C).

There remained a thin (1 to 2 mm) layer of fixed tissue which was adherent to the underlying normal tissue (fig 1 B). The lesion was covered with a

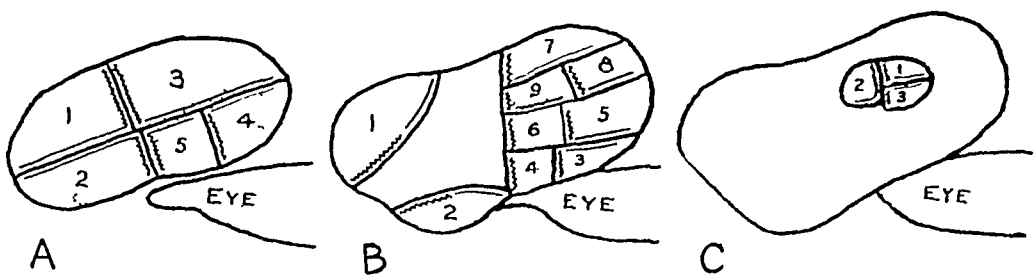


Fig 2—Maps showing the locations of specimens removed on the second, third and fourth days from the lesion pictured in figure 1. Microscopically located areas of cancer are stippled.

petrolatum gauze dressing. One week later the final layer of fixed tissue had separated except for a small area of exposed nasal bone in the center (fig 1 C). (The average time for separation of fixed tissue from the eyelids is six days, with limits of two to eleven days, previous irradiation slows separation.) Since the bone was slow to separate, owing to the previous irradiation, no drastic attempt was made to remove it. Granulation tissue spread across the bone, and the lesion healed uneventfully, with a good cosmetic and functional result (fig 1 D).

With careful chemosurgical technic, there is practically no danger of damaging the eyeball. The edema of the lids and the chemosis which result from the chemical inflammation tend to push the treated area away from the eyeball, and the tears dilute and carry away the fixative as it slowly permeates the eyelid.

The protective function of the tears is particularly evident in the treatment of cancer of the portion of the upper eyelid that overlies the cornea. In a number of cases the full thickness of the upper eyelid in this region was chemosurgically excised, and in no case was the eyeball damaged (figs 11 and 14).

In 1 case, in which there was a large carcinoma of the middle of the upper lid, a hole 3 mm in diameter resulted from its chemosurgical excision so that the patient peered through the hole when his eye was closed (fig 14). However, in spite of the action of the fixative on the lid directly over the cornea, there was no damage to the eye. Incidentally, the hole closed and the cosmetic result was practically perfect.

While the tears serve to protect the eyeball from damage by the fixative, they may also be a nuisance in that they may wet the dressings and carry the fixative away from the area under treatment. This difficulty is most likely to be encountered in the treatment of cancer at the lid margins, where the fixative may cause excessive tearing by making contact with the conjunctival surface. To obviate this difficulty, the fixative is applied to the skin only, if the conjunctiva is involved by the cancer, it is treated by approaching it from the cutaneous side of the eyelid. In some instances it is helpful to keep the eye closed under an eye patch.

Large portions of the eyelids may be removed without damage to the eyeball, but, of course, if the entire upper eyelid is removed, it is difficult to prevent the complications arising from exposure of the eyeball. The entire lower lid can be removed however, without complications (fig 7).

If the eyeball itself is extensively involved by the carcinoma, it must be removed (figs 10 and 15). In 4 cases in this series surgical enucleation was done either before or after chemosurgical treatment while in 3 cases the eye was chemosurgically removed.

Chemosurgical removal of the eye also has been carried out during the chemosurgical excision of a number of extensive cancers which arose on the nose, forehead, temple or cheek. The operation is readily accomplished. For example in the case of the patient shown in figure 15, the fixative was applied to the medial side of the eyeball which had been deeply invaded by the cancer. On the following day the fixed sclera was removed and the vitreous humor evacuated. The fixative was then reapplied to the medial side of the eye and also to the interior of the eye. During the next four days the eye was removed by working from the medial side. The eyelids were partially preserved (fig 15 B and C).

In some cases it is desirable to cocaine the conjunctiva and quickly destroy the entire conjunctiva with dichloroacetic acid before proceeding with the chemosurgical removal of the eye. This is done because, while the eyeball itself is relatively insensitive, the conjunctiva is, of course, highly sensitive.

In a few earlier cases of this series, the scar contraction resulted in eversion of the eyelid with exposure and irritation of the palpebral conjunctiva (fig 9 C). This complication may be avoided by the simple

expedient of removing the full thickness of the eyelid in cases in which the lid margin is appreciably involved. When this is done, the portion of the eyelid is pulled up into approximately normal position by the contraction of the scar (figs 4, 6, 8 and 13)

When a large portion of the eyelid is removed, plastic repair may be desirable. Fortunately, the tissues are well vascularized and healthy after chemosurgical treatment, hence, they lend themselves well to such procedures.

Carcinomas which extend back of the orbital rim have a strong tendency to creep along close to the bony wall of the orbit. This phenomenon is most frequently seen with lesions involving the inner canthal region, but it is also fairly common in the floor of the orbit. By means of the chemosurgical technic these extensions often may be removed without damaging the eyeball. When the periosteum is involved, it is, of course, necessary to fix also a thin layer of bone, this fixed bone separates in about three weeks. If the cancer involves much of the floor of the orbit, the eyeball may drop a little after chemosurgical treatment, but, surprisingly, the extraocular motions are little impaired.

When the cancer extends much more than 2 cm into the orbit, it may be necessary to remove the eye to obtain sufficient exposure. In several such instances the carcinoma was followed back to the inferior orbital fissure. If it extends through this fissure, further chemosurgical treatment is contraindicated.

#### THERAPEUTIC RESULTS IN CASES OF BASAL CELL CARCINOMA OF THE EYELID

A total of 80 basal cell carcinomas of the eyelid were chemosurgically excised during the six year period ending Oct 28, 1943, which date is over three years prior to the time of this writing.

*End Results After Three Years or More*—The 80 cases were divided into "indeterminate" and "determinate" groups according to the classification of Martin, MacComb and Blady.<sup>7</sup> The indeterminate group is composed of 18 cases in which the patients either died of other causes or were lost from observation without recurrence. The determinate group is composed of 62 cases in which there were obtained either unsuccessful results (4 cases) or successful results (58 cases).

In the 62 cases of the determinate group the rate of cure after three years or more was 93.5 per cent (table 1).

*End Results After Five Years or More*—The end results for the five year period were evaluated for 60 consecutive cases, of which

<sup>7</sup> Martin, H. E., MacComb, W. S., and Blady, J. V. Cancer of the Lip, *Ann Surg* 114:341 (Sept) 1941.

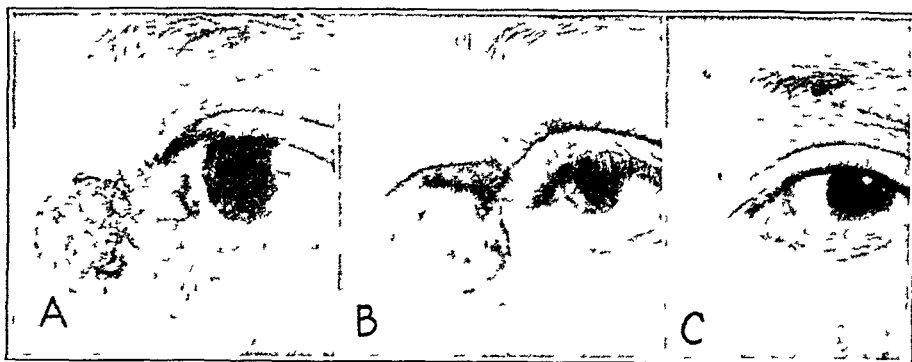


Fig 3—*A*, basal cell carcinoma of group C (average diameter, 2 to 3 cm) in the inner canthal region *B*, granulation tissue after the cancer had been removed in four microscopically controlled stages and after removal of the final layer of fixed tissue *C*, healed lesion The patient had been free of cancer for five years at the time of this report.



Fig 4—*A*, basal cell carcinoma of group A (average diameter, under 1 cm) on the lower lid, near the inner canthus It extended into the palpebral conjunctiva *B* granulation tissue after separation of the final layer of fixed tissue, showing the relatively large amount of tissue that had to be removed to eradicate the cancer, which had extended much farther than was clinically apparent The full thickness of the lid at its margin was removed to avoid eversion *C*, healed lesion At the time of this report, four years later, there is no evidence of cancer



Fig 5—*A*, basal cell carcinoma of group A, located several millimeters below the margin of the lid near the outer canthus *B*, granulation tissue after separation of the final layer of fixed tissue *C*, healed lesion There was no evidence of cancer when the patient died, after three and one-half years

13 were in the indeterminate group and 47 were in the determinate group. Of the latter group, there were successful results in 43 cases, and the rate of cure for the five year period was 91.5 per cent (table 1).

TABLE 1—*End Results of Chemosurgical Treatment of Basal Cell Carcinoma of the Eyelids After Periods of Three Years and Five Years*<sup>\*</sup>

	Three Year Period	Five Year Period
Total number of patients	80	60
Indeterminate group		
Patients who died of other causes without recurrence	11	8
Patients lost from observation without recurrence	7	5
Total number	18	13
Determinate group, total number	62	47
Unsuccessful results		
Patients dead, cancer present at time of death	2	2
Patients lost from observation, with cancer	2	2
Patients living, with cancer		
Total number	4	4
Successful results		
Patients free from cancer for three years or more	58	
Patients free from cancer for five years or more		43
Three year end results		
Total number of patients with successful results divided by total number of patients in determinate group (58 — 62)	93.5%	
Five year end results		
Total number of patients with successful results divided by total number of patients in determinate group (43 — 47)		91.5%

\* This series includes the cases of all patients with histologically proved basal cell carcinomas, both early and advanced, previously untreated and recurrent, who were admitted to the chemosurgical clinic during the period from Aug. 14, 1937 to Oct. 28, 1943, for the three year group, and during the period from Aug. 14, 1937 to Sept. 19, 1941, for the five year group.

TABLE 2—*Relation of Size of Basal Cell Carcinoma to Prognosis*

Group	Average Diameter, Cm.	Number of Lesions	Successful Results	
			Number	Percentage
A	Under 1	31	31	100
B	1-2	22	21	95.5
C	2-3	5	4	80
D	3 or more	4	2	50
All groups		62	58	93.5

*Effect of Size of Lesion on Prognosis*—The 62 cases in the determinate group in the three year period were divided into four groups according to the average diameter of the lesion: A, under 1 cm (figs 4, 5 and 11), B, 1 to 2 cm (figs 1, 6, 8 and 12), C, 2 to 3 cm (figs 3 and 7), and D, 3 cm or more (figs 9 and 10). It should be mentioned that the recorded sizes are those initially measured, the actual

size of the cancer, as determined by means of the microscopically controlled excisions, was often much larger

As would be expected, the prognosis was, to some extent, influenced by the size of the lesion (table 2). However, extensiveness per se is not a contraindicatory factor for the chemosurgical treatment of basal cell carcinoma of the eyelid unless the neoplasm has extended into the cranial cavity. Other factors, such as old age, poor general health or uncooperativeness, were more influential than the size of the lesion in

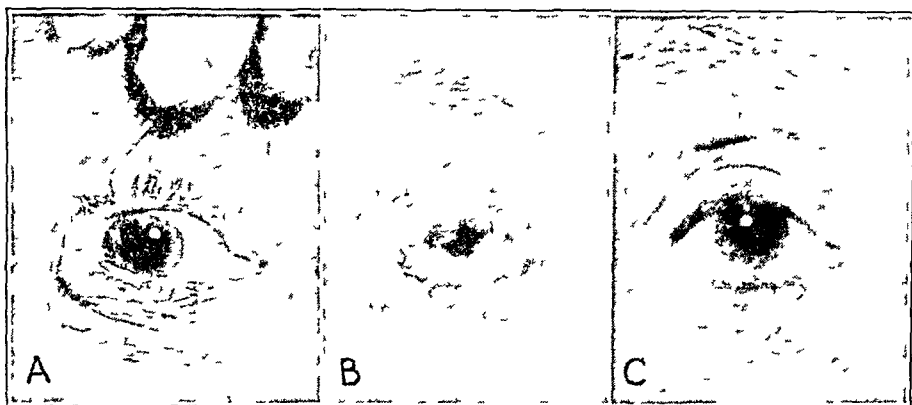


Fig 6—*A*, basal cell carcinoma of group B (average diameter, 1 to 2 cm), located near the outer canthus. *B*, granulation tissue after chemosurgical excision of the cancer, which involved the full thickness of the lid. *C*, healed lesion. There was no evidence of cancer when the patient died, after two and one-half years.

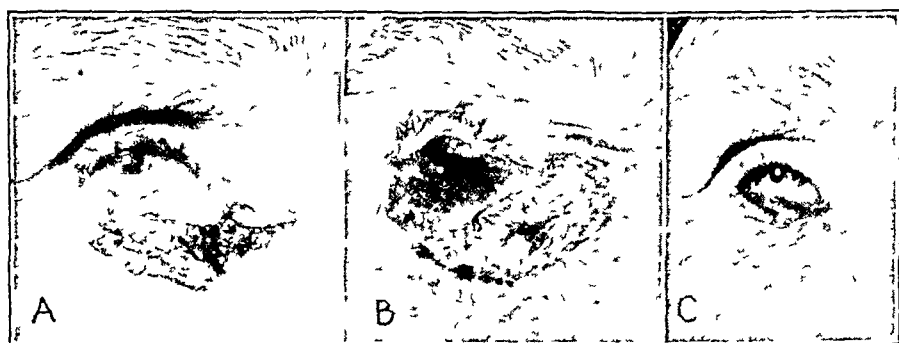


Fig 7—*A*, basal cell carcinoma of group C. It was of twenty years' duration and had recurred after roentgen ray treatment. *B*, granulation tissue laterally and adherent fixed tissue medially, in the inner canthal region, where the carcinoma had eroded deeply. *C*, healed lesion. There was no evidence of cancer when the patient died, after six years.

the decision to cease treatment before the cancer was eradicated in the 4 cases in this series in which treatment was unsuccessful.

*Effect of Previous Unsuccessful Treatment on Prognosis*—Of the 62 cases in the determinate group in the three year period, there had been previous unsuccessful surgical treatment or irradiation in 20 cases

(32.3 per cent) The rate of cure for the group with previous treatment was only 85 per cent, as compared with 97.6 per cent for the group with no previous treatment (table 3)

However, the lower rate of cure for the group with previous treatment does not mean that previous treatment per se constitutes an unfavorable prognostic factor. It is more likely that the delay occasioned by the previous inadequate treatment, with consequent deep and exten-

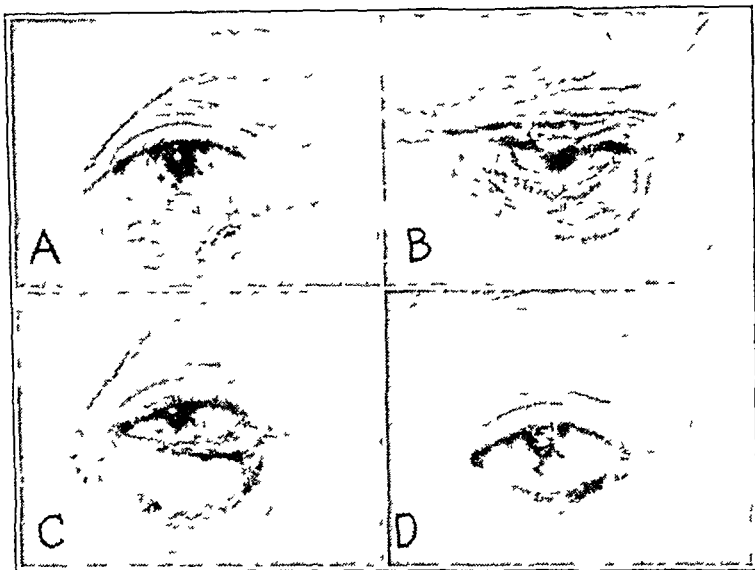


Fig 8—*A*, basal cell carcinoma of group B. *B*, thin layer of adherent fixed tissue after four days, when a microscopically cancer-free plane had been reached. *C*, granulation tissue after the final layer of fixed tissue was removed, after five days more. *D*, healed lesion. The slight degree of ectropion could have been largely avoided if the full thickness of the lid margin had been removed. The patient is still free of cancer, after six years.

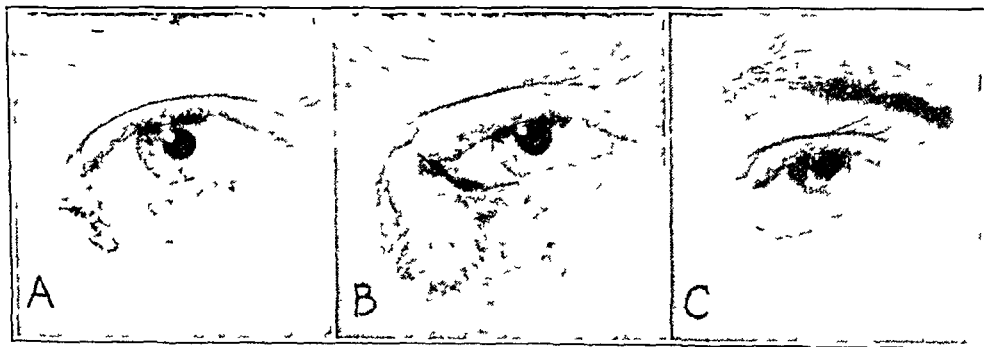


Fig 9—*A*, basal cell carcinoma of group D (average diameter, over 3 cm), located on the lower lid in the outer canthal region. The cancer had continued to spread despite roentgen irradiation, electrodesiccation, cauterization with silver nitrate and radium treatments, over a period of seven years. *B*, granulation tissue after removal of the cancer in four microscopically controlled stages and after separation of the final layer of fixed tissue. *C*, healed lesion. The downward retraction of the lid could have been avoided by the removal of the full thickness of the lid margin, so that the upward pull of the scar in this region would counteract the downward pull of the scar inferior to the lid margin. There is no evidence of cancer, after five years. The ectropion does not bother the patient enough to cause him to return for the suggested repair.



sive spread of the cancer, has an unfavorable influence on prognosis. As a matter of fact, the most urgent indication for chemosurgical treatment is in the case in which other methods have failed.

*Effect of Degree of Invasiveness on Prognosis*—To give some idea of the degree of malignancy, it is convenient to classify basal cell carcinomas as "invasive" or "noninvasive." Microscopically, the invasive basal cell carcinoma exhibits slender, invasive strands of cancer cells which actively erode the normal tissues and produce a more or less



Fig 10—*A*, basal cell carcinoma of group D. The cancer, which was of fifteen years' duration, had been held in check superficially by means of fourteen radium treatments, over a period of seven years. *B*, granulation tissue after removal of the cancer, which involved the entire maxillary sinus, part of the nasal bone and so much of the tissue in the floor of the orbit that the eye had to be enucleated during the course of chemosurgical treatment. *C*, healed lesion, showing antrum lined with mucosa. The patient is still free of cancer, after eight years. *D*, reconstruction of the cancerous mass, showing clinically visible portion (central dark area) and palpable portion (light area). The extensions into the orbit, onto the nasal bone and into the maxillary sinus are also shown.

copious reaction of the connective tissue stroma. On the other hand the noninvasive carcinoma is composed of clumps of cancer cells which are well demarcated from the normal tissues, which as a rule contribute

little connective tissue stroma. There are numerous intergradations, so that it is sometimes difficult to decide in which group a given lesion belongs.

Clinically, the "invasive" carcinoma is apt to be the ingrowing, rodent ulcer type of lesion, while the "noninvasive" carcinoma is usually the outgrowing, nodular type.

TABLE 3—*Effect of Previous Unsuccessful Treatment of Basal Cell Carcinoma on Prognosis*

	Number of Patients	Successful Results	
		Number	Percentage
Previously treated	20	17	85
Previously untreated	42	41	97.6

TABLE 4—*Effect of Histologic Degree of Invasiveness of Basal Cell Carcinoma on Prognosis*

	Number of Lesions	Successful Results	
		Number	Percentage
Invasive	29	25	86.2
Noninvasive	33	33	100

TABLE 5—*Effect of Site of Origin of Basal Cell Carcinoma on Prognosis*

Site	Number of Lesions	Successful Results	
		Number	Percentage
Upper eyelid	17	16	94.1
Lower eyelid	29	29	100
Inner canthus	10	8	80
Outer canthus	6	5	83.3

That the noninvasive cancers are less dangerous than the invasive lesions is attested by the fact that 100 per cent of the former were cured, whereas 86.2 per cent of the invasive cancers were eradicated (table 4). However, it is in the treatment of the highly invasive lesions that the chemosurgical technic is of particular value, because it provides a means of following out the deep-seated, often unsuspected outgrowths characteristic of this type.

*Effect of Site of Origin on Prognosis*—The most frequent site of origin of basal cell carcinoma was the lower eyelid, and 100 per cent of the cancers in this location were cured (table 5). The next most frequent site was the upper eyelid, and a high proportion of these lesions were also cured (94.1 per cent). However, the uncommoner cancers

which originated in the canthal regions carried a somewhat less favorable prognosis (outer canthus, 83.3 per cent, inner canthus, 80 per cent). These findings are consistent with the notoriously invasive nature of basal cell carcinoma in these locations, particularly in the inner canthus. However, the prognosis in the canthal lesions is appreciably improved by the use of the chemosurgical method, with its microscopic control of excision.

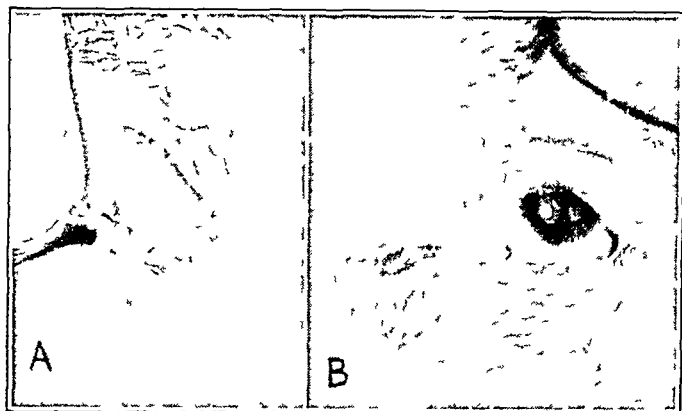


Fig 11—*A*, basal cell carcinoma, group A. The cancer involved the full thickness of the portion of the upper lid overlying the cornea. *B*, healed lesion. There was no evidence of cancer when the patient died, after five years.

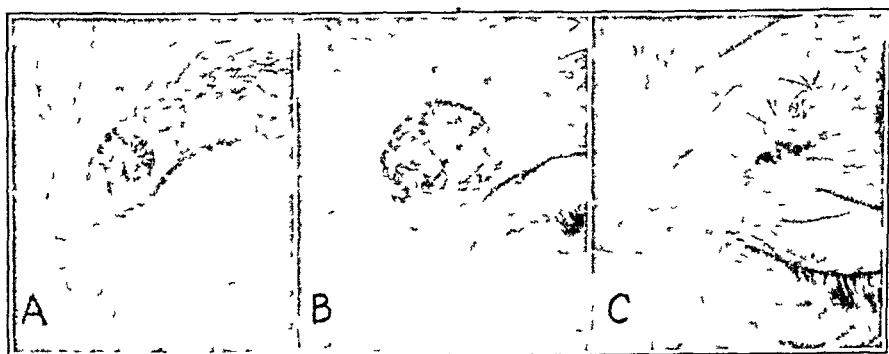


Fig 12—*A*, basal cell carcinoma of group B, located on the upper lid and the adjacent brow. *B*, granulation tissue after separation of the final layer of fixed tissue. *C*, healed lesion. The patient is free of cancer, after five years.

#### THERAPEUTIC RESULTS IN CASES OF SQUAMOUS CELL CARCINOMA OF THE EYELID

Squamous cell carcinoma being a relatively uncommon lesion of the eyelids, only 19 were chemosurgically treated during the six year period from May 12, 1937 to April 19, 1943, the latter date being over three years prior to this writing. The primary lesion in every case was successfully treated, but in 1 case fatal metastasis developed.

*End Results After Three Years or More*—The end results after an observation period of three years or more were evaluated for the 19 consecutive cases in this group. There were 3 cases in the indeterminate category, leaving 16 cases in the determinate group. In the latter group there were 15 cases in which the treatment was successful and 1 in which it was unsuccessful. Thus, the rate of cure for the three year period was 93.8 per cent (table 6).

*End Results After Five Years or More*—There were 13 cases in the group in the five year period, and of these, 11 were in the determinate group. There was 1 case in the latter group in which treatment was unsuccessful. Thus, the rate of cure for the five year period was 90.9 per cent (table 6).

*Factors Which Influence the Prognosis*—Among the factors which would be expected to influence the prognosis in cases of squamous cell carcinoma of the eyelid are size of lesion, previous treatment, histologic

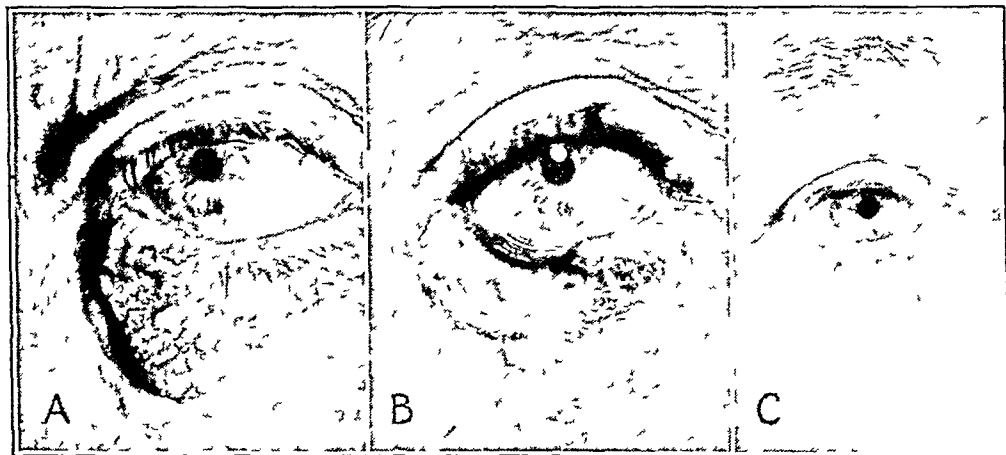


Fig 13—A, squamous cell carcinoma of group B, of grade 1 malignancy (Broders' classification). B, granulation tissue after separation of the final layer of fixed tissue. C, healed lesion.

grade of malignancy, site of origin and presence or absence of metastasis. Since the series is small and there was only 1 case in which treatment was unsuccessful, the data are insufficient to justify tabulation of the results as affected by these factors.

The distribution of the cases as regards the size of the lesion was as follows: group A (average diameter, under 1 cm), 9 cases; group B (1 to 2 cm), 4 cases; group C (2 to 3 cm), 2 cases; and group D (3 cm or more), 1 case. The case in which treatment was unsuccessful was in group B, and the conclusion is that size per se was not an important factor in this series. However, if the lesion were so extensive that vital structures, such as the brain, were involved, the prognosis would, of course, be affected.

Previous unsuccessful therapy would be expected to affect prognosis in that it might cause a delay in chemosurgical treatment, with conse-

quent increase in extensiveness and increase in likelihood of metastasis. In this series only 1 patient had received previous treatment. The patient who died of cancer had not had previous treatment.

The carcinomas in the 16 cases of the determinate group in the three year period were classified according to Broders' four grades of malignancy, as follows: grade 1, 11 lesions; grade 2, 3 lesions; grade 3, 1 lesion; and grade 4, no lesions. In the 1 case in which treatment failed the carcinoma was of grade 3 malignancy. The poorer prognosis occasioned by higher degrees of malignancy is largely due to the increased likelihood of metastasis.

TABLE 6—*End Results for Squamous Cell Carcinoma of the Eyelids After Periods of Three Years and Five Years\**

	Three Year Period	Five Year Period
Total number of patients	19	13
Indeterminate group		
Patients who died of other causes without recurrence	2	1
Patients lost from observation without recurrence	1	1
Total number	3	2
Determinate group, total number	16	11
Unsuccessful results		
Patients dead, cancer present at time of death	0	0
Patients lost from observation, with cancer	1	1
Patients living, with cancer	0	0
Total number	1	1
Successful results		
Patients free from cancer for three years or more	15	
Patients free from cancer for five years or more		10
Three year end results		
Total number of patients with successful results divided by total number of patients in determinate group (15 — 16)	93.8%	
Five year end results		
Total number of patients with successful results divided by total number of patients in determinate group (10 — 11)		90.9%

\* This series includes the cases of all patients with histologically proved squamous cell carcinoma, both early and advanced, previously untreated and recurrent, who were admitted to the chemosurgical clinic during the period from May 12, 1937 to April 10, 1943, for the three year group, and during the period from May 12, 1937 to Jan. 19, 1943, for the five year group.

Of the 16 cases of squamous cell carcinomas in the determinate series, the lesion originated on the lower eyelid in 12 cases and on the upper eyelid in 4 cases. In none did it arise in the canthal regions. In the 1 case in which treatment was unsuccessful the carcinoma arose on the lower lid, but no definite conclusions can be drawn as to the effect of the site of origin on prognosis.

Metastasis was the complication responsible for the unsuccessful result in 1 case. The lesion, which had a malignancy of grade 3, was located on the lower eyelid at the junction with the cheek. This primary

lesion did not recur after chemosurgical treatment, but on a check-up visit two years later, a large, fixed submaxillary mass was found. This had appeared while the patient supposedly was being kept under observation by the family physician. Presumably, this mass was a metastatic lesion, although it was impossible to rule out the possibility of its having originated as a primary lesion of the submaxillary salivary gland, which

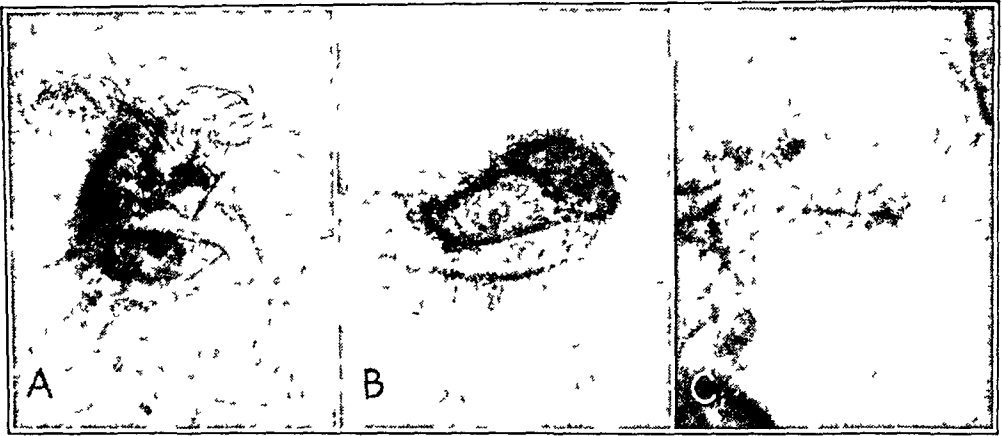


Fig 14—*A*, squamous cell carcinoma of group B, of grade 2 malignancy. *B*, granulation tissue and hole through the full thickness of the eyelid directly over the pupil after separation of the final layer of fixed tissue. *C*, healed lesion. The hole closed spontaneously within one month. The patient is free of cancer, after five years.

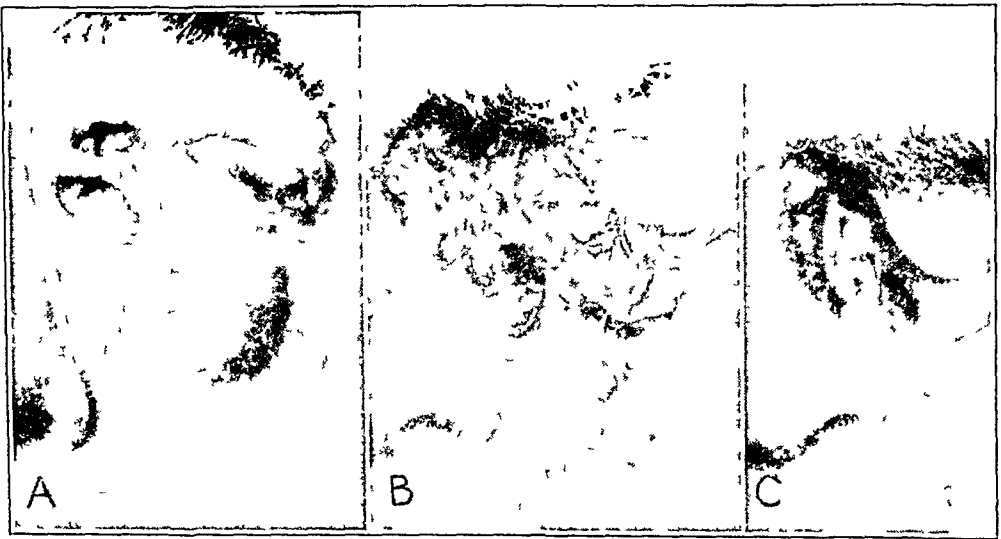


Fig 15—*A*, squamous cell carcinoma of group D. The degree of malignancy was grade 3. *B*, granulation tissue after separation of the final layer of fixed tissue, following removal of the cancer in eighteen microscopically controlled stages. The medial rectus muscle and the medial portion of the sclera were eroded through by the cancer, so that the eyeball was chemosurgically removed. The cancer also had eroded through the nasal bone into the nasal mucosa and through the maxillary bone into the antrum. *C*, healed lesion. The defect was closed with a graft after a year, and there is no evidence of cancer, after five years.

it involved. The mass was radically excised by means of the chemosurgical technique, but the growth recurred, and the patient presumably

died of cancer. There was no recurrence of the primary lesion when the patient was last seen, three and one-half years after chemosurgical excision. This case emphasizes the importance of insisting on particularly close observation of patients with squamous cell carcinoma.

The question of the desirability of prophylactic dissection of regional lymph nodes may occasionally arise. It would seem that a fairly large lesion with a grade of malignancy of high 2 or higher should lead one to consider the advisability of a prophylactic dissection.

#### THERAPEUTIC RESULTS FOR OTHER LESIONS OF THE EYELIDS

The microscopic control of excision afforded by the chemosurgical method is also of value in the removal of other neoplasms and of precancerous lesions affecting the eyelids. The following lesions were successfully treated: hemangioma, pigmented nevus, radiation ulcer, seborrheic keratosis and senile keratosis (7 cases).

In 5 cases the senile keratosis had become papillated, and no doubt were undergoing malignant change in some cases. It is in the treatment of these lesions in which it is difficult to determine grossly whether or not cancer is present that the microscopic control of the chemosurgical technic is particularly valuable.

#### COMMENT

In the course of the treatment of the 99 carcinomas reported on here, it became evident that cancers of the eyelid, particularly those in the inner canthal region, are often unpredictable in the direction and extent of their invasion into the normal tissues. Frequently, small caliber, grossly undetectable extensions from the main cancerous mass occur, and it is only by means of the microscopic control afforded by the chemosurgical technic that these outgrowths can reliably be removed without excessive destruction of normal tissue.

That the method is uncommonly reliable is indicated by comparison with the best series in the literature, as regards both excellence of results and adequate statistical analysis, namely, that of Magnusson.<sup>8</sup> The results reported by this author were obtained with the use of the highly developed radiologic, surgical and electrosurgical technics used at *Radiumhemmet* in Stockholm. From his protocols, it was determined that the rate of cure for the three year period for all types of cancer of the eyelid was 89.5 per cent. In the present series, the rate of cure for the same interval was 93.6 per cent. Both series were practically identical as regards the per cent of cases in the two larger

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<sup>8</sup> Magnusson, A. H. W., *Skin Cancer. A Clinical Study with Special Reference to Radium Treatment*, Acta radiol., 1935, supp. 22, p. 1.

groups (15 per cent) and as regards the per cent of the lesions which were recurrent after previous treatment (27 per cent)

This reliability of the chemosurgical method is not attained by excessively radical excision. Quite the contrary, no more than 1 or 2 mm of tissue beyond the points of cancerous involvement is removed. When undesirable defects do occur, owing to extensive carcinomatous invasion, they are relatively readily repaired because the remaining tissues are well vascularized and healthy. Moreover, since a maximum amount of normal tissue is preserved there is more tissue to work with in making a repair.

The safety of the eyeball during the course of chemosurgical treatment of cancer of the eyelids is an important advantage. In this series, no bulbar damage occurred except with those lesions which actually invaded the eyeball. The protective effect of the edema of the lid, the chemosis and the flow of tears is responsible for this safety.

Chemosurgical treatment entails practically no mortality. In this series there were no deaths during treatment despite the fact that many of the patients were old and in poor general health.

Some lesions of the eyelid are technically difficult to excise chemosurgically, and experience with the method is advisable before the treatment of these lesions is undertaken.

#### SUMMARY AND CONCLUSIONS

The chief advantage of the chemosurgical treatment of cancer of the eyelid is the microscopic control of excision afforded by the method. This control is responsible for both the great reliability and the conservatism of the method.

The reliability of the method is attested by the high rates of cure. Thus, for basal cell carcinoma, successful results were attained in 93.5 per cent of the 62 cases in the three year period and in 91.5 per cent of the 47 cases in the five year period. For squamous cell carcinoma, the rate of cure was 93.8 per cent for the 16 cases in the three year period and 90.9 per cent for the 11 cases in the five year period.

The reliability of the method is not attained at the expense of conservatism, for only 1 or 2 mm of tissue beyond the points of carcinomatous invasion is removed.

The method is also effective in the removal of various benign neoplasms and precancerous lesions of the eyelids.

State of Wisconsin General Hospital



# ANIRIDIA CONGENITA

Report of Five Cases, Genealogy, Possibilities of Treatment

MORRIS H. PINCUS, M.D.

BROOKLYN

AT THE Industrial Home for the Blind, Brooklyn, I examined 5 patients with bilateral aniridia. Inasmuch as this is a rare congenital condition,<sup>1</sup> it was believed that a report of these cases, including the genealogy and the possibilities of treatment, would be of interest.

## REPORT OF CASES

CASE 1—J. K. Sr., aged 57, of Irish descent, had had poor vision since birth. Except for a mild degree of diabetes, which was controlled by diet, he was in good health.

His forehead was furrowed. Bilateral ptosis was present. A circumcorneal fringe of superficial blood vessels penetrated the cornea of each eye, but the pupillary portions were clear. The anterior chambers were deep in appearance. No iris was visible in either eye with reflected light, but with the slit lamp a very small tag of iris tissue was just barely seen at the superior temporal angle of both the right and the left eye. The zonule was not visible. Each lens revealed anterior cortical, as well as dense nuclear, changes. A fundus glow (reflex) was present in the right eye, but no details were discernible. There was no fundus glow in the left eye. The ocular movements of each eye were normal, even though an esotropia of approximately 25 degrees was present in the left eye. Ocular tension (McLean) was 23 mm. of mercury in the right eye and 23 mm. in the left eye.

Vision was 5/200 in the right eye and was limited to perception of hand movements at 1 foot (30 cm.) in the left eye.

There was no improvement in vision in either eye with lenses.

CASE 2—The patient's son, J. K. Jr., aged 23, was a robust, physically normal man, he had had poor vision since birth (fig. 1).

His forehead was furrowed. The palpebral fissures were narrow, owing to slight ptosis. A fine horizontal and a coarse rotary nystagmus were present. The corneas were clear. The anterior chambers were deep. No iris tissue was visible in either eye by reflected light or with the slit lamp. A number of small opacities were scattered throughout the anterior and the posterior cortex of each lens. Owing to the nystagmus, details of the fundus were not distinct, but each disk appeared pale, the blood vessels attenuated and the macular area dull (no

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<sup>1</sup> Duke-Elder W. S. Text-Book of Ophthalmology, London, Henry Kimpton, 1938, vol. 2, pp. 1298-1302.

reflex) The ocular movements revealed the presence of double hypertropia Ocular tension (McLean) was 38 mm of mercury in the right eye and 40 mm in the left eye.

Vision was 14/200 in the right eye and 11/200 in the left eye

CASE 3—Mr E H, aged 24, of Jewish descent, apparently in good health, (fig 2), was born with bilateral ptosis and poor vision

His brow was furrowed Bilateral ptosis, more conspicuous on the left side, was present. A fine horizontal nystagmus existed Both corneas were clear The anterior chambers were deep, and no iris tissue was visible in either eye by reflected light or with the slit lamp Each lens revealed symmetrically placed, coralliform opacities in the posterior cortex, but the central area was clear The margins of the lens were distinctly seen, and the zonule appeared normal In spite of the nystagmus, a fairly good view of each fundus was possible The disk in each eye was very small and appeared pale The blood vessels were attenuated

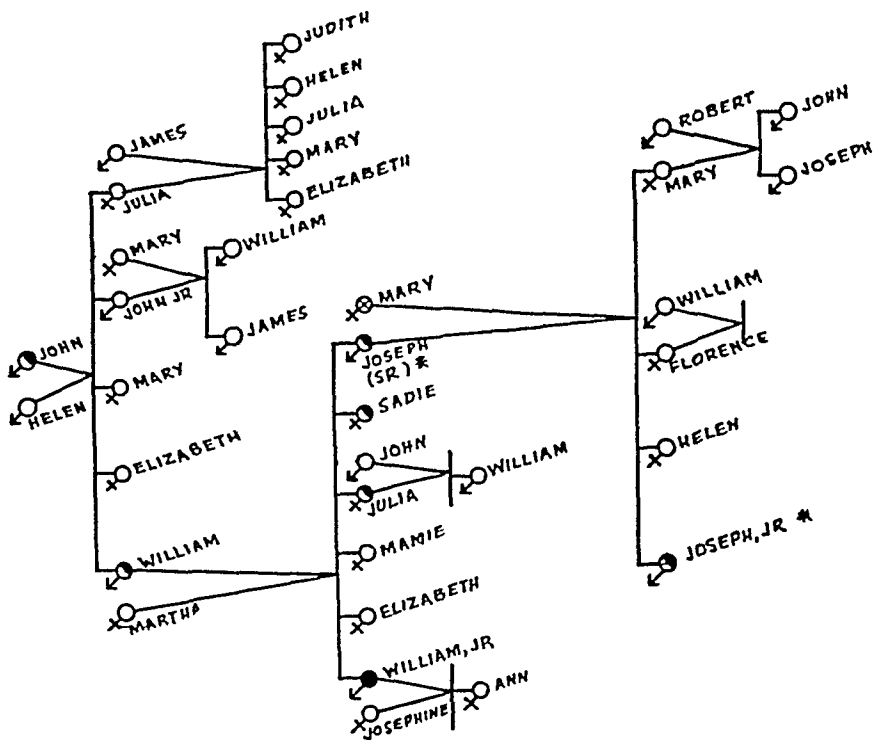


Fig 1—Genealogic chart of the J K family (case 2)

In this chart, and in the accompanying charts, normal eyes are indicated by clear circles, the presence of aniridia is shown by half black circles, blindness of one eye, due to a fall, by a black circle, blindness of one eye, of unknown cause, by a circle with cross, and blindness of both eyes, cause unknown, by a circle with question mark The asterisk indicates that the case was presented in the text

and the maculas dull No other abnormalities were noted Ocular movements were normal Ocular tension (McLean) was 35 mm of mercury in the right eye and 40 mm in the left eye

Vision was 16/200 in the right eye and 15/200 in the left eye

CASE 4—J M Q, aged 42, a well built, healthy white man, of Irish descent, had had poor vision since birth (fig 3) The palpebral fissures were narrow A fine horizontal nystagmus was present Each cornea had a number of nebulous opacities, with the blood vessels from the inferior limbus infiltrating the stroma The anterior chambers appeared deep, and no iris tissue was visible in either eye by reflected light or with the slit lamp Each lens was visible in its entirety

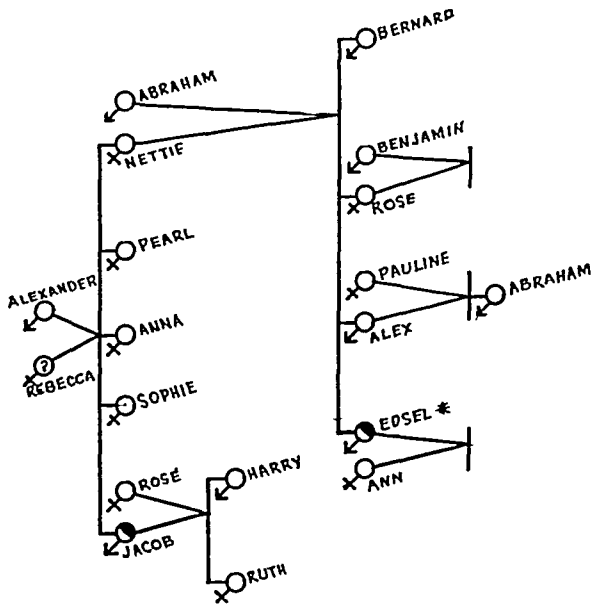


Fig 2—Genealogic chart of E H family (case 3)

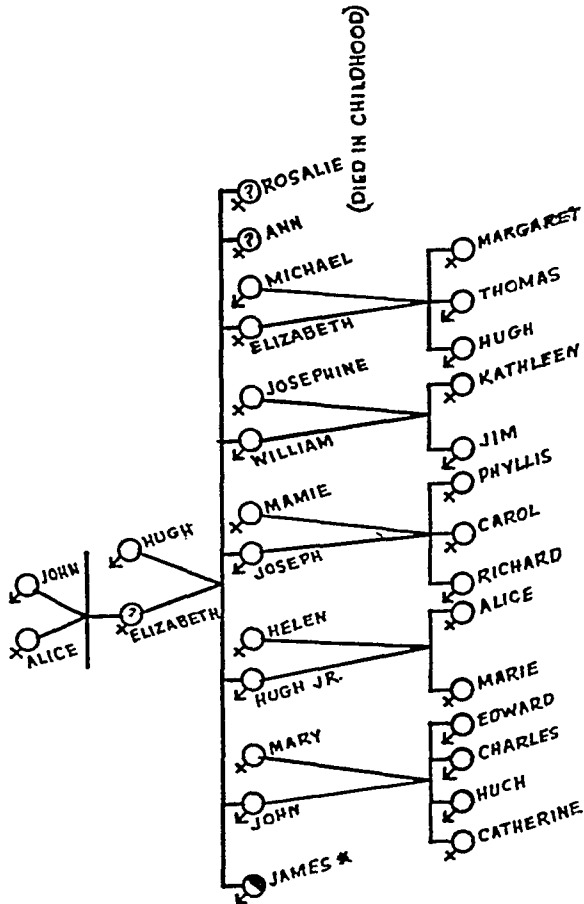


Fig 3—Genealogic chart of J M Q family (case 4)

It was yellowish, and the nuclear and posterior cortical regions were rather opaque. There was a dull fundus glow in each eye, but no details were visible. Ocular movements were normal. Ocular tension (McLean) was 30 mm of mercury in the right eye and 30 mm in the left eye.

Vision was 3/200 in the right eye, light perception with good projection was present in the left eye.

There was no improvement in either eye with lenses.

- CASE 5—G. C., aged 27, of Italian descent, had always had poor vision (fig. 4)

He had slight ptosis of both upper lids, moderate frontal furrowing and pronounced horizontal and rotary nystagmus. The periphery of both corneas was invaded with fine blood vessels. The anterior chambers were deep and no iris tissue was visible in either eye on superficial examination, but with the slit lamp a small stump of iris was seen in the lower temporal angle of each eye. Brownish pigmented particles were visible on the anterior surface of the lens capsule. A few anterior and posterior cortical opacities were present. Owing

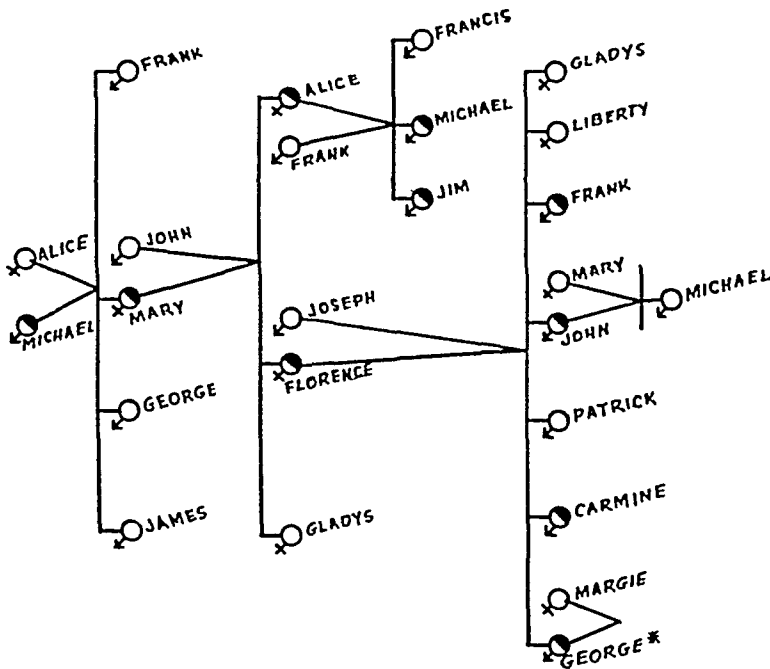


Fig. 4—Genealogic chart of G. C. family (case 5)

to the nystagmus, details of the fundus could not be visualized. Ocular movements were normal. Ocular tension (McLean) was 30 mm of mercury in the right eye and 30 mm in the left eye.

Vision was 11/200 in the right eye, improved to 15/200 with a correction of  $-4.00$  sph  $\subset -0.50$  cyl, axis 30 and 11/200 in the left eye, improved to 15/200 with a correction of  $-2.00$  sph  $\subset -0.75$  cyl, axis 180.

#### COMMENT

The clinical picture of aniridia is characteristic. The most obvious features of the condition are the furrowing of the brow, the narrowing of the palpebral fissures, the photophobia and the appearance of an unusually large pupil, generally associated with very poor vision and frequently accompanied with nystagmus.

The low visual acuity has been accounted for by the fact that on a number of clinical examinations the fovea was observed to be absent<sup>2</sup> This absence was confirmed histologically<sup>3</sup> Alger,<sup>4</sup> however, expressed the opinion that the poor vision is due to the aberration of the light rays entering the eye in the regions both outside and inside the equator of the lens He stated

it [the fovea centralis] does not develop fully until 16 weeks after birth Just what causes it to develop after birth is not known, but it is probably due to the light striking it and stimulating it In the case of aniridia, the light is not concentrated at the macula in a clear pattern of an image and the stimulation of the macula does not take place as it would in ordinary eyes Consequently, the macula would not have a tendency to form in the normal fashion<sup>4</sup>

Glaucoma as a secondary complication is not uncommon<sup>5</sup> The association, however, is not invariable Dennis<sup>6</sup> noted that physostigmine almost invariably controls the increased ocular tension accompanying aniridia He suggested that the tension is probably lowered by reason of the well known power of this drug to contract blood vessels

In all reported histopathologic examinations<sup>7</sup> of aniridic eyes, a small rim of iris tissue of variable degree is observed encircling the periphery The iris tissue is rudimentary, and the musculature is absent or very poorly developed The pigment epithelium may be plicated at the free border and may overlap the stump of the iris as an ectropion The trabeculae at the root of the iris are frequently anomalous, and the iris may be adherent to the cornea, so that the angle of the anterior chamber is obliterated Although the obliteration of the angle is not invariable, it may account for the complication of glaucoma The ciliary processes may be normal, but they are frequently small, aplastic or absent The lens may be ectopic, cataractous or small Persistent vessels of the vascular tunic of the lens have been noted The retina may

2 Vogt, A Ueber angeborenes und vererbtes Fehlen der Macula lutea, *Klin Monatsbl f Augenh* **72**:806, 1924 Duke-Elder<sup>1</sup>

3 (a) Seefelder, R Die Aniridie als eine Entwicklungshemmung der Retina, *Arch f Ophth* **70** 65, 1909 (b) Holm, E Ein anatomisch untersuchter Fall von Aniridie, *Klin Monatsbl f Augenh* **66** 730, 1921

4 Alger, L G Cause and Treatment of Poor Vision in Aniridia, *Am J Ophth* **28** 730, 1945

5 (a) Collins, E T Aniridia and Glaucoma, *Ophth Rev* **10** 101, 1891 (b) Neher, E M Aniridia Congenita, Irideremia Report of Cases Extending Through Five Generations, *Am J Ophth* **21** 293, 1938 (c) Hudson, A C Congenital Aniridia Treated by Sclero-Corneal Trephining, *Tr Ophth Soc U Kingdom* **41** 274, 1921

6 Dennis, D N Double Congenital Aniridia with Glaucoma and Cataract Extraction with Resulting Good Vision, Observations on the Action of Eserin Where the Iris Is Absent, *Arch Ophth* **35** 527, 1906

7 Collins, E T, and Mayou, M S Pathology and Bacteriology of the Eye, in Pyle, W L An International System of Ophthalmic Practice, Philadelphia, P Blakiston's Son & Co, 1911, pp 75-79 Duke-Elder<sup>1</sup> Footnote 3

show abnormalities, such as degeneration in the periphery, changes in the ganglion cells and absence of the fovea centralis

The hereditary tendency of aniridia is pronounced, the anomaly behaving as a dominant characteristic<sup>8</sup> Figures 1 to 4 corroborate this observation The anomaly is not sex linked There is no racial or national predilection

Many theories have been advanced to explain the occurrence of aniridia<sup>1</sup> The preponderance of evidence substantiates the congenital nature of the condition,<sup>9</sup> the mechanism reducing itself to failure in development of the retinal ectoderm or to aberrant development of the vascular mesoderm<sup>1</sup> Possibly both factors are operative in different cases Neher<sup>5b</sup> stated

Cognizance is taken of the fact that mesodermic tissue passes forward normally around the equator of the lens to join the anterior mesodermal ingrowth, not only in the region of the fetal cleft, but in all directions Its presence is normal, and it gives way to the iris as the latter grows in from all sides, offering no resistance except where the mesoderm is hyperdeveloped or possibly over-vascularized Should only a strand of tissue be thus affected, a coloboma is formed If the whole tissue is hyperresistant, the iris cannot grow as it normally does and aniridia results

As has already been mentioned, poor vision is one of the prominent features of this condition Although nothing can be done to correct the aniridia, several useful procedures are available to help unfortunate persons with this defect to obtain and to maintain useful vision Alger<sup>4</sup> tattooed the periphery of the corneas of a 20 month old child with typical aniridia, and two years later reexamination revealed 20/20 vision in the left eye and somewhat less in the right eye

Dennis,<sup>6</sup> Blue<sup>10</sup> and Bieringer<sup>11</sup> obtained useful vision after the extraction of a cataractous lens

Reid<sup>12</sup> obtained 6/6 vision in an adult with typical congenital aniridia by the use of contact glasses containing an opaque brown corneal portion with a 2.5 mm clear central pupil These glasses were worn comfortably for twelve hours a day

Hudson<sup>5c</sup> reported the case of a 7 week old child, with bilateral aniridia, who had edema of the cornea, a dull fundus reflex and

8 Wood, C. A. The American Encyclopedia of Ophthalmology, Chicago, Cleveland Press, 1913, vol 1, p 483 Croll, L. J. Aniridia Occurring in Three Generations, Arch Ophth 2 699 (Dec) 1929 Risley, S. D. Hereditary

9 Mann, I. Coloboma Iridis and Its Embryology, Tr Ophth Soc U Aniridia An Interesting Family History, J A M A 64 1310 (April 17) 1915 Duke-Elder<sup>1</sup> Alger<sup>4</sup> Neher<sup>5b</sup>

Kingdom 44 161, 1924 Seefelder<sup>3a</sup> Neher<sup>5b</sup> Collins and Mayou<sup>7</sup>

10 Blue, J. B. Bilateral Aniridia, Am J Ophth 5 483, 1922

11 Bieringer, S. Linsenextraktion bei Aniridie, Klin Monatsbl f Augenh 88 744, 1932

12 Reid, A. M. Case of Congenital Aniridia Fitted with Pigmented Contact Glasses, Tr Ophth Soc U Kingdom (pt 1) 58 434, 1938

increased intraocular pressure in the right eye. A paracentesis was performed, and the cornea cleared almost immediately. One week later a corneoscleral trephination was performed. The intraocular tension became satisfactory, and the fundus reflex returned to normal brightness.

With these tried methods of treatment at hand, I felt that improvement in the visual acuities of patients 1 and 4, who have mature cataracts, would best be accomplished by extracting the lenses. To date, however, these patients have postponed surgical intervention.

The right eyes in cases 2, 3 and 5 were tested with a trial contact lens which possessed an opaque corneal periphery and a 4 mm clear central pupil. The results are as follows:

Case 2 Vision (O D) 14/200, improved to 20/200 with the trial contact lens and —1.00 D sph

Case 3 Vision (O D) 16/200, improved to 20/200 with the trial contact lens and —3.00 D sph

Case 5 Vision (O D) 11/200, improved to 20/200 with the trial contact lens and —2.00 D sph

The improvement of vision in each of these cases would tend to support the theory that aberration of light entering the eye is responsible in great measure for the poor visual acuity in aniridia.

#### SUMMARY

Five cases of bilateral aniridia, with the genealogic charts and a discussion of the possibilities of treatment, are presented. Aniridia is an uncommon congenital anomaly, is almost always bilateral and appears as a dominant characteristic. It is not sex linked, nor is there a national or racial predilection.

The clinical and pathologic features are a furrowed brow, narrow palpebral fissures, unusually large pupils, photophobia, poor vision and, frequently, nystagmus. Pathologically, a small rim of iris tissue, of variable degree, is always observed encircling the periphery. The apparent absence of the iris on clinical examination is due to the fact that a short stump is hidden behind the corneoscleral margin. Other ocular defects, such as ptosis, muscular imbalance, corneal disturbances, lenticular anomalies and retinal pathologic changes are common. Glaucoma, as a secondary complication, is not uncommon.

Several useful procedures are available to help unfortunate persons with this defect to obtain and to maintain useful vision. In order to be effective, treatment should be started early in life. Tattooing of the outer portions of the cornea, extraction of a cataractous lens and the wearing of an opaque contact lens with a 3 to 4 mm, clear central pupil are the methods of choice. Glaucoma, as a secondary complication, can be controlled with physostigmine or by corneoscleral trephining.

# HUMAN CONJUNCTIVA GRAFTED ON THE CHORIO-ALLANTOIS OF CHICK EMBRYOS

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AND

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**I**N THIS study we report an attempt to graft human conjunctiva on the chorioallantois of chick embryos according to the method developed by Goodpasture and associates for the human skin<sup>1</sup>

## TECHNIC

The conjunctival sac was anesthetized by instillation of 1 drop of a 4 per cent solution of cocaine hydrochloride. An oval piece of conjunctiva, 7 to 8 mm long and about 2 to 3 mm wide, was excised with scissors from the lower fornix and transferred into 2 cc isotonic solution of sodium chloride containing 50 Oxford units of penicillin per cubic centimeter. The fragments of conjunctiva suspended in this solution were placed in a refrigerator for four to six hours.

Fertile hens' eggs kept in an incubator for eight to eleven days were used in the grafting experiments. The eggs were candled, and the places corresponding with the air bubble and the large membrane vessels were marked on the shell. The egg was placed on a stand of plasticine, the shell cleansed with alcohol, and a window of 1 cm square cut with a rotating carborundum disk, according to the method of Goodpasture and Buddingh<sup>2</sup>. The shell was perforated at the location of the air bubble with a sterile needle and the air aspirated with a small rubber balloon. In this way, the fibrous membrane was separated from the adherent chorioallantoic membrane of the shell, making it possible to cut the fibrous membrane without injuring the chorioallantois in the majority of cases.

For the purpose of grafting, a piece of conjunctiva 2 to 3 mm square was spread on the blade of a cataract knife and carefully deposited on the chorioallantois at the site of the large membrane vessels. The shell window was framed with hot paraffin and sealed hermetically with a cover glass. The opening made by the needle over the air bubble was also closed with paraffin. The egg was then placed in an incubator held at a temperature of 38 C.

Twenty-four hours later the cover glass was lifted and 0.2 cc (containing 300 Oxford units) of a solution of penicillin was instilled on the chorioallantoic mem-

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1 Goodpasture, E W, Douglas, B, and Anderson, K. Study of Human Skin Grafted Upon Chorio-Allantois of Chick Embryos, *J Exper Med* **68** 891, 1938.

2 Goodpasture, E W, and Buddingh, G J. Preparation of Antismallpox Vaccines by Culture of Virus in Chorio-Allantoic Membrane of Chick Embryos, and Its Use in Human Immunization, *Am J Hyg* **21**.319, 1935.



brane near the graft. This procedure was repeated forty-eight hours later. Usually after six days the experiments were concluded. After the cover glass was removed and the shell window widened, the graft was excised, together with the adherent chorioallantoic membrane. The excised specimen was spread on filter paper, fixed in Zenker's solution and embedded in a paraffin-pyroxylin mixture, and the sections were stained with hematoxylin and eosin and with Mallory's anilin blue stain for collagen.

All manipulations were carried out with aseptic precautions. Before and after the grafting, bacteriologic tests were performed.

#### OBSERVATIONS

*Macroscopic Appearance*—At the end of the six day period of incubation the conjunctival graft could be clearly seen as a button-like prominence, recognizable by its pinkish color. In the region of the graft, the vessels of the chorioallantoic membrane were distinctly widened and appeared to be more numerous. The graft was either wholly adherent with a broad base or protruded mushroom-like on a more or less broad pedicle (fig 1).

*Microscopic Appearance*—Histologic examination revealed a number of peculiarities of the epithelium of the conjunctiva, the subepithelial tissue and the blood vessels of the conjunctival transplant, as well as the adjacent chorioallantoic membrane, these will be described in detail.

*Epithelium* The epithelial cover of the transplanted piece of conjunctiva in most cases was well preserved. In some instances it appeared in its normal thickness, in others it was thickened (fig 2), chiefly, however, it was thinned so as to form now and then only one layer (figs 3 and 6). The cellular architecture of the epithelium, although in places preserved without change, was usually altered, the arrangement in layers not being always clearly discernible. In both the thickened and the thinned portions of the epithelium the regular position of the nuclei was disturbed and the normally vertical position of the nuclei of the surface layer was missing from the picture. When the epithelium was thinned, the axes of the cell nuclei were more or less parallel with the surface.

The individual epithelial cell fairly constantly presented a normal appearance, with unchanged structure of the nucleus and the cytoplasm, and showed normal staining capacity. The individual cell was usually well demarcated, sometimes, however, especially in the deeper layers, the cell membrane became indistinct, the cells coalescing to form a syncytium. Frequently the cells of the epithelial cover appeared dissociated. The surface epithelial layer was often interspersed with normal mucus-containing goblet cells (figs 3 and 4 C).

There was no distinct division between the epithelium and the subepithelial tissue in the majority of cases. The border was often indented, groups of epithelial cells seeming to penetrate rather deeply



Fig 1—*A*, mushroom-like conjunctival graft on chorioallantois seven days after transplantation Hematoxylin-eosin stain,  $\times 31$

*B*, pedunculated conjunctival graft five days after transplantation, showing a great number of wide blood vessels engorged with chick erythrocytes Hematoxylin-eosin stain,  $\times 60$

into the subepithelial tissue. These epithelial downgrowths were solid or contained cystlike spaces.

Frequently, the epithelial cover was infiltrated with chick polymorphonuclear leukocytes (figs 3 and 7). Here and there were seen

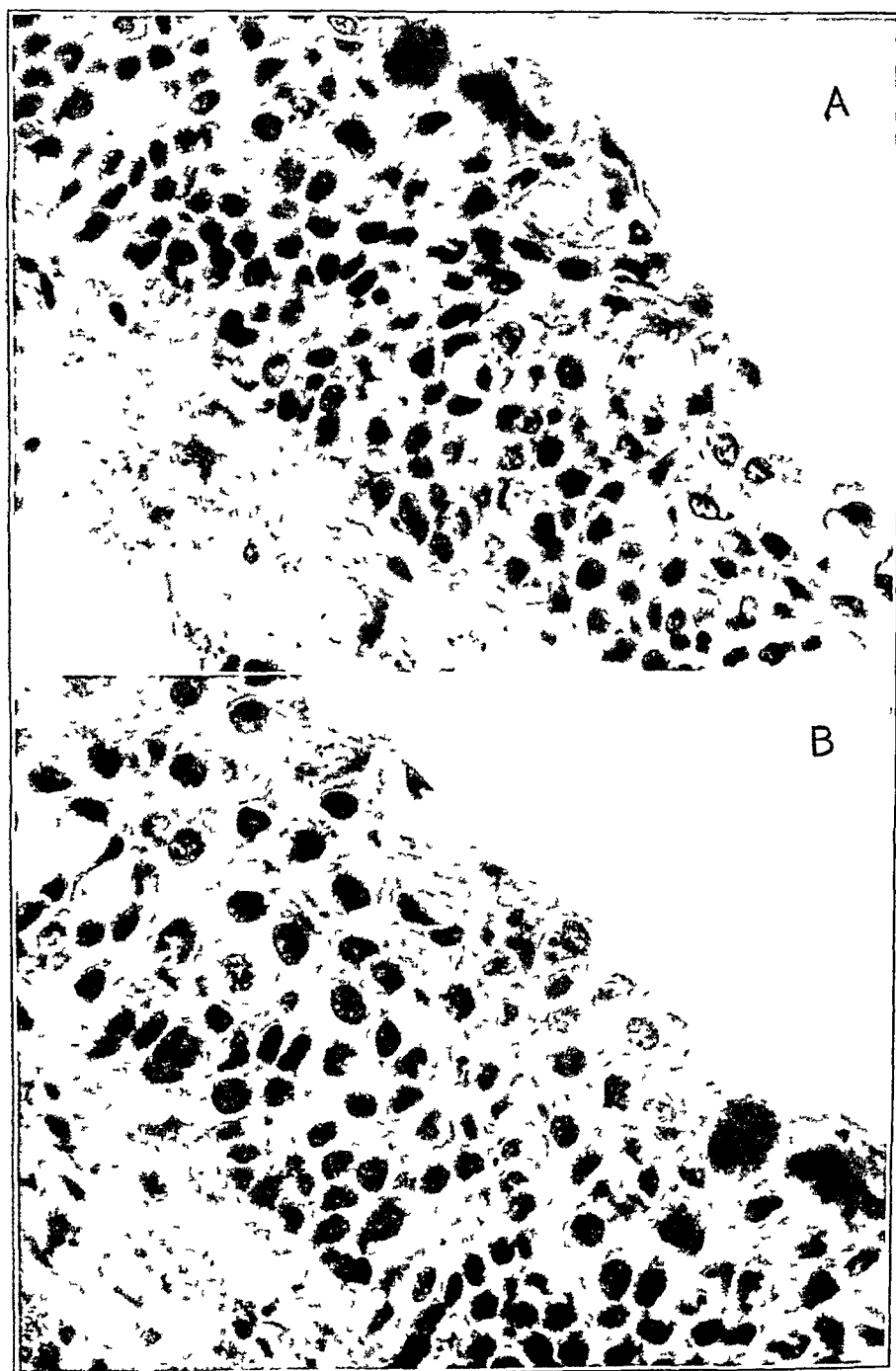


Fig 2—*A*, conjunctival graft five days after transplantation, showing greatly thickened epithelial layer. Hematoxylin-eosin stain,  $\times 605$ .

*B*, Section similar to *A*.

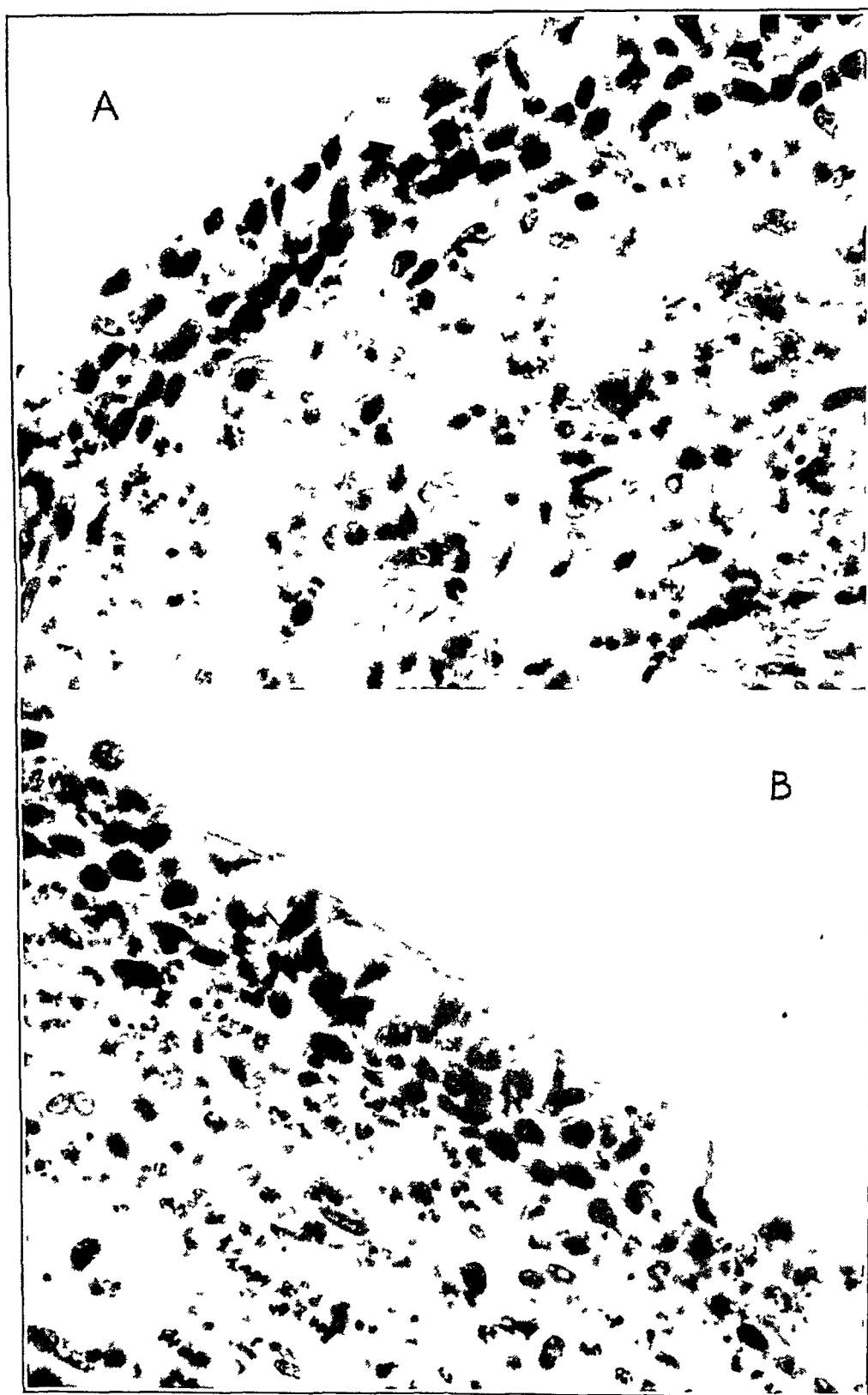


Fig 3—*A*, conjunctival graft five days after transplantation, showing epithelial layer with numerous goblet cells and leukocytic infiltration of subepithelial tissue. Hematoxylin-eosin stain,  $\times 610$

*B*, Section similar to *A*,  $\times 500$

cystlike spaces in various layers of the epithelium, filled with leukocytes (fig 7 *B*) Occasionally intracellular leukocytes, chiefly within large vacuoles, were seen in dissociated epithelial cells (fig 4 *D*) In several grafts, however, there was no leukocytic infiltration Numerous mitotic figures were noted in all layers of the conjunctival epithelium (fig 4 *A* and *B*)

**Subepithelial Conjunctival Tissue** The subepithelial connective tissue was usually well preserved, showing a variable content of cells, the fixed connective tissue cells being generally enlarged and swollen

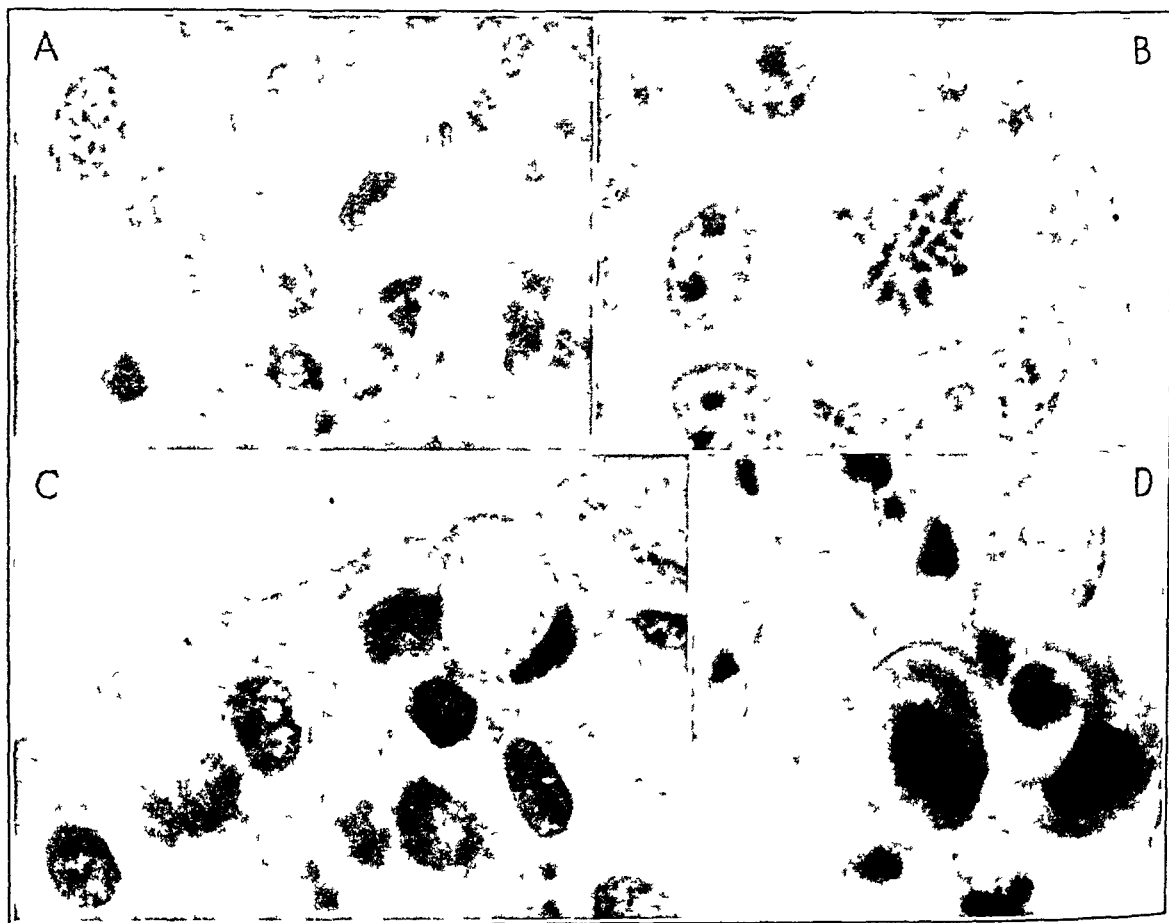


Fig 4—*A*, conjunctival graft five days after transplantation showing mitoses in the epithelium Hematoxylin-eosin stain  $\times 1,200$

*B*, conjunctival graft five days after transplantation, showing mitosis in an epithelial cell Hematoxylin-eosin stain,  $\times 1,775$

*C*, conjunctival graft six days after transplantation, showing surface epithelial layer with a goblet cell Hematoxylin-eosin stain  $\times 1,360$

*D*, conjunctival graft six days after transplantation, showing a group of dissociated epithelial cells, one of them containing a polymorphonuclear leukocyte situated in a vacuole Hematoxylin-eosin stain,  $\times 1,365$

(fig 5) The number of mononuclear cells was not increased The stroma contained a dense meshwork of collagen fibers, often it presented a hyalin appearance The transition from the subepithelial connective

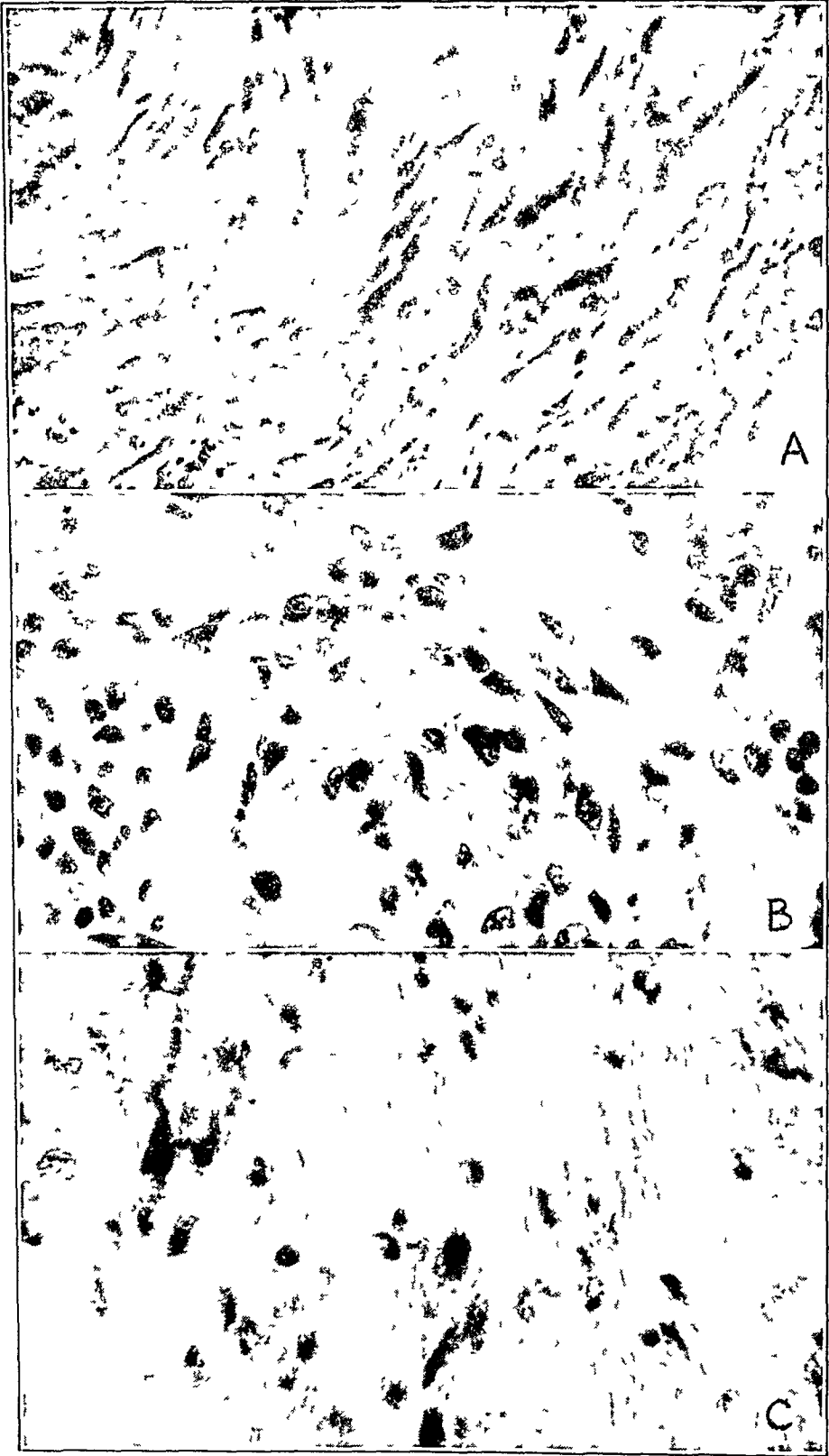


Fig 5—A, B and C, conjunctival grafts six days after transplantation, showing subepithelial connective tissue with varying cellular content. Hematoxylin-eosin stain,  $\times 640$

tissue into the mesodermal fibrous tissue of the membrane was continuous

In a considerable number of grafts a scanty infiltration with polymorphonuclear leukocytes was observed, the cells accumulating mainly at

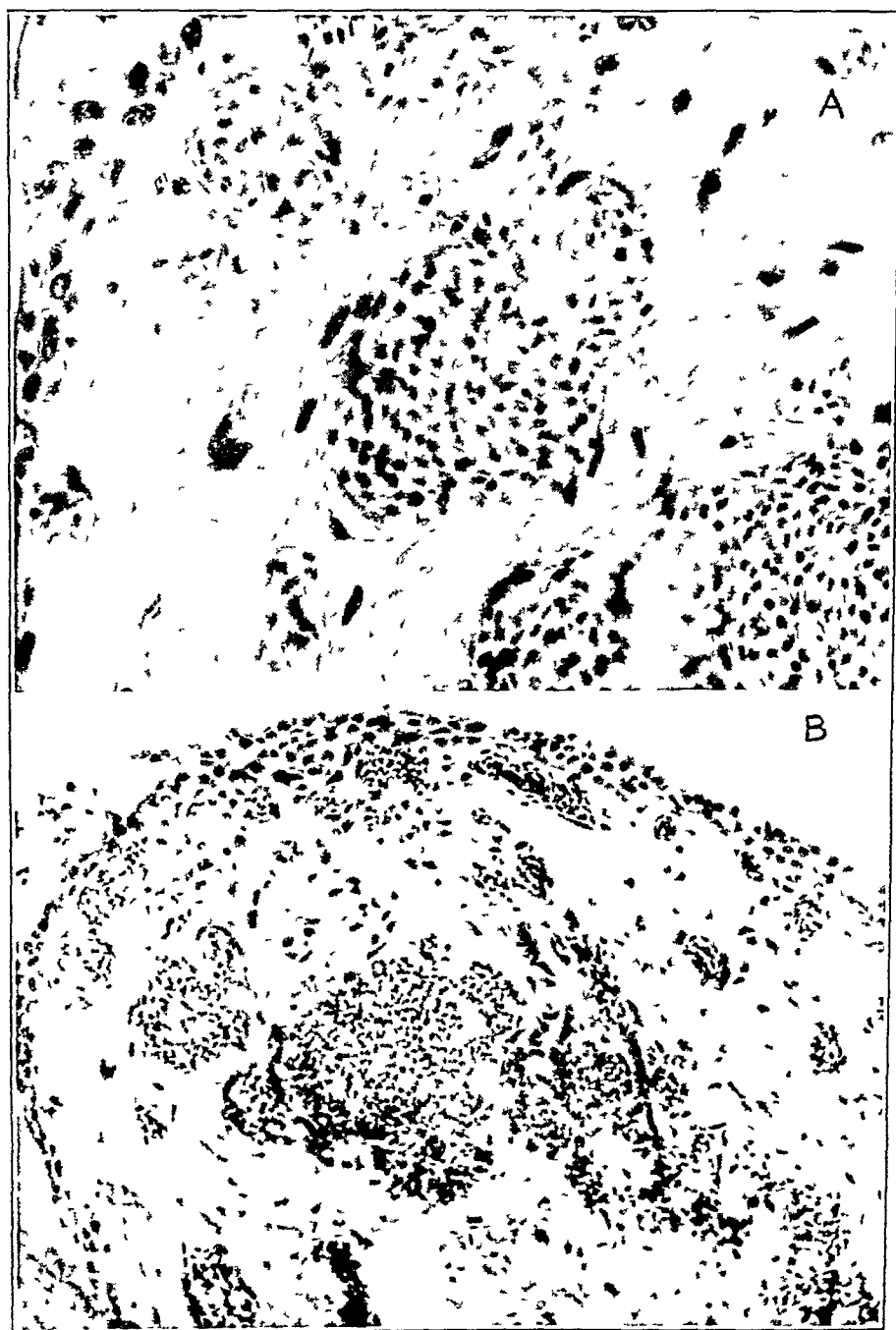


Fig 6—*A*, conjunctival graft six days after transplantation. Blood vessels containing chick erythrocytes reach the epithelium. Hematoxylin-eosin stain,  $\times 400$

*B*, section similar to *A*,  $\times 190$

the border between the epithelium and the subepithelial tissue (fig 6 C) Sometimes the infiltration was massive and the epithelium appeared elevated, as by a vesicle (fig 7 A) In some of the grafts small and sharply delimited necrotic areas were encountered within the subepi-



Fig 6 (cont) —C, section similar to A,  $\times 520$  D, section similar to A,  $\times 240$

thelial tissue Frequently the tissue was entirely free from leukocytic infiltration.

**Blood Vessels** The grafts fairly constantly showed an abundance of wide capillaries (fig 1 B) It could easily be perceived that the capil-





Fig 7—*A*, conjunctival graft six days after transplantation, with massive leukocytic infiltration beneath the epithelial cover and cystic spaces within the epithelium. Hematoxylin-eosin stain,  $\times 295$ .

*B*, conjunctival graft six days after transplantation, with cystic spaces within the epithelial layer, some of them containing polymorphonuclear leukocytes. Hematoxylin-eosin stain,  $\times 700$ .

layers of the graft were one with the capillaries of the chorioallantoic membrane. The capillaries arising from the chorioallantois penetrated the graft, approaching the epithelium, and some of the finest branches even invaded the epithelial cover (fig 6)

The capillaries of the graft were lined with endothelial cells, which at times were flat and at others cubical. The capillaries were engorged with nucleated chick red blood cells. Here and there vessels contained human red blood cells, and occasionally erythrocytes of both species persisted in the lumens of the capillaries.

**Chorioallantoic Membrane** Where the graft became adherent, the chorioallantois completely lost its ectodermal cover. At the margin of the graft the chorioallantoic ectoderm joined the conjunctival epithelium, each maintaining its own character. The chorioallantois remained in most cases well preserved, showing no reactive changes even when the graft became necrotic. Only rarely were there seen necrotic areas, walled off with giant cells, or foci of infiltration with polymorphonuclear leukocytes. Numerous epithelial pearls of various sizes were observed at different levels of the chorioallantoic membrane, but sometimes they were entirely absent.

#### COMMENT

The experiments reported here show that it is possible to maintain human conjunctiva in fairly healthy condition outside the body by grafting conjunctival fragments onto the chorioallantoic membrane of developing chick embryos. These grafts, examined after a period of five to six days, showed that all tissue elements of the conjunctiva were without substantial alteration.

The survival of the transplanted conjunctiva on the chorioallantoic membrane is due, no doubt, to the fact that the graft is quickly incorporated into the vascular system of the chorioallantois, from which it derives a continuous nutritional supply. In the achievement of this close connection an important role is played both by the extraordinary abundance of blood vessels in the chorioallantois and by the loose texture of the subepithelial connective tissue of the conjunctiva. Numerous proliferating capillaries invade the graft, reach the epithelium and frequently even penetrate its layers. The frequent observation of both human and nucleated chick erythrocytes in the vessels of the graft suggests that the vascular system of the conjunctiva has become connected with that of the chick embryo.

The rich nutritional supply granted by quick and abundant vascularization creates conditions enabling the conjunctiva to survive in its entirety. Both conjunctival layers, the epithelium and the subepithelial tissue, retain their structure and show no regressive changes. In the epithelium numerous mitoses are encountered.

The pathologic feature noted most frequently in the conjunctival graft is the infiltration with polymorphonuclear leukocytes, which is usually moderate but may sometimes become intense. There is no doubt that the leukocytes infiltrating the graft originate in the chick embryo. As the infiltration occurs in sterile grafts, its frequent incidence cannot be interpreted otherwise than as a response of the host to the foreign tissue. It is remarkable that this infiltration apparently does not interfere with the survival and maintenance of the graft.

The changes just described refer to successful grafts, but it must be emphasized that successful "takes" were in no way the general rule. The main obstacle, not easily overcome, is the microbial flora of the conjunctiva. After transplantation, the native micropopulation of the conjunctiva, originally limited in number, causes infection of the chick embryo, leading finally to disintegration of the graft and death of the host. Although penicillin is a powerful agent in controlling the bacterial infection, it fails in some cases (penicillin-resistant microbes).

A further disturbing feature is the tendency of some grafts to sink into the mesoderm of the membrane. Such grafts as a rule eventually become necrotic.

In spite of these unfavorable factors, the number of successful "takes" is sufficiently large to warrant experiments on a larger scale without serious inconvenience. The method presented in this paper seems to offer possibilities of a systematic study of histogenesis in the conjunctiva in various pathologic conditions, with the exclusion of somatic factors. The chief field of application of this method will most probably be the study of morbid conditions caused by viruses affecting the human conjunctiva, for whose maintenance *in vitro* human tissue is indispensable.

#### SUMMARY

Experiments are reported in which fragments of human conjunctiva were grafted on the chorioallantoic membrane of developing chick embryos.

The technic, as well as the macroscopic and microscopic appearance of the graft, is described.

It is demonstrated that with this method of grafting onto chorioallantoic membrane it is possible to maintain human conjunctiva in fairly good condition during the experimental period (six to seven days). Both the epithelial and the subepithelial tissues appear well preserved. Numerous mitotic figures may be noted in the cells of the epithelial layer. In addition, the graft is largely invaded by blood vessels derived from the chorioallantois.

Infiltration of the graft with polymorphonuclear leukocytes is encountered frequently. This infiltration is due not to infection but to the

response of the host to the foreign tissue, and does not interfere with the survival of the graft

The chief obstacle to be overcome in these experiments is native infection of the conjunctiva, which can be controlled only to a certain extent with the use of penicillin

The method presented seems to offer possibilities of a systematic study, under conditions excluding somatic factors, of the histogenesis of pathologic changes of the conjunctiva in various diseases, especially those caused by viruses

NOTE—Only after completion of the paper did we become aware of experiments performed by Julianelle,<sup>3</sup> who grafted human conjunctival cells (from scrapings) containing demonstrable trachomatous virus on the chorioallantois of the developing chick embryo. The epithelial cells were observed to be proliferating, unaccompanied with multiplication of the virus itself

Dr L. Doljanski, head of the Department of Experimental Pathology, Hebrew University, was of great assistance during this investigation, and Mrs Irma Parnes gave technical aid

15 Abyssinian Street

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3 Julianelle, L. A. Studies on the Infectivity of Trachoma. XII. Additional Observations on the Cultivability of the Virus, *Am J Ophth* **26**:280 (March) 1943

# UNILATERAL SYPHILITIC PRIMARY ATROPHY OF THE OPTIC NERVES

An Anatomic Study of Two Cases

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UNILATERAL syphilitic primary optic nerve atrophy will almost always become bilateral if not treated properly. If, however, therapy is begun while the atrophy of the optic nerve is limited to one side, involvement of the normal eye may be prevented in a high proportion of cases.<sup>1</sup>

In my anatomic material of 12 cases of syphilitic primary optic nerve atrophy, death had occurred at a time when the atrophy was confined to one optic nerve in 2. The histologic study of the visual pathways in these 2 cases furnished the clue to the ultimate degeneration of the nerve fibers of both optic nerves.

## REPORT OF CASES

*CASE 1—Unilateral syphilitic primary atrophy of the optic nerve in a patient with dementia paralytica*

A Negro woman aged 65 presented the characteristic symptoms of dementia paralytica without tabetic involvement of the spinal cord. There were syphilitic aortic insufficiency and roentgenographic evidence of beginning aneurysm of the arch of the aorta. An aneurysm of the right innominate artery was also present.

Both pupils were small and fixed to light. The patient, who showed advanced mental deterioration, did not complain of loss of vision, and atrophy of the left optic nerve went unnoticed by both the patient and the physician.

The Wassermann, Kahn and Kline reactions of the blood and the Wassermann reaction of the spinal fluid were positive. The Ross-Jones and Pandy tests gave a 4 plus reaction. The cell count of the spinal fluid was 202 per cubic millimeter. The colloidal gold test read 5555543210.

On account of the patient's advanced age and the presence of syphilitic involvement of the aorta, malarial and other antisyphilitic therapy was withheld. The patient died four months after admission of dementia paralytica, complicated by cardiovascular syphilis.

*Postmortem Observations*—Several fine bands of the slightly thickened basilar arachnoid passed over both optic nerves and the optic chiasm. There was no sign

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1 Moore, J. E., Woods, A. C., Hopkins, H. H., and Sloan, L. L. The Treatment of Syphilitic Primary Optic Atrophy, J. A. M. A. **111** 385 (July 30) 1938.

of constriction of or pressure on either of the optic nerves by the arachnoidal bands. The left optic nerve was reduced in volume and was grayish. The left side of the chiasm was also somewhat atrophic.

*Histologic Examination*—Left, Atrophied, Optic Nerve. Demyelination was complete except for a small area of fairly normal-staining nerve fibers. This area was situated in the periphery and could be traced in this location throughout the length of the optic nerve (fig. 1). In the pia of the intracranial portion of the left optic nerve was much inflammatory exudate, consisting of lymphocytes and plasma cells. This exudate diminished rapidly along the course of the nerve through the optic foramen and was absent in the pia of the orbital portion. In the interior of the intracranial portion—both in the demyelinated part and, to a lesser degree, in the area with the still normal nerve fibers—there was perivascular round cell infiltration in the sheaths of the larger vessels and in the walls of the capillaries. Such inflammatory exudate was absent in the interior of the orbital portion of the left optic nerve.



Fig. 1 (case 1)—Unilateral syphilitic primary atrophy of the optic nerve in a patient with dementia paralytica. The upper picture shows the base of the brain with the intracranial portions of both optic nerves. There is demyelination of most of the left optic nerve, which is much reduced in size. In the right optic nerve there is already a minute area of demyelination. The optochiasmatic arachnoid passes harmlessly over both optic nerves.

The lower picture represents the orbital portions of the left and right optic nerves. There is a small, peripherally arranged area with normal nerve fibers in the otherwise demyelinated left optic nerve. The right optic nerve shows beginning marginal demyelination, which extends at one place far into the interior of the nerve.

*Right Optic Nerve*. There was beginning marginal demyelination, which at one place extended a considerable distance into the interior of the nerve. In the pia of the intracranial portion a round cell infiltration, similar to that in the left, atrophied, optic nerve, was present but the exudate was much less intense. In the demyelinated marginal area there was moderate round cell infiltration, which continued in a slighter degree throughout the diameter of the optic nerve.

**Optic Chiasm** At the level where the two optic nerves merged with the chiasm there was about the same pronounced degree of round cell infiltration in the pia of the two nerves. A somewhat smaller amount of exudate was present in the pia of the chiasm. However, within the chiasm plasma cells and lymphocytes could be detected only with the use of high power objectives. The cells were scattered in an even fashion throughout the entire width of the chiasm, with less syphilitic infiltration in the interior of the chiasm than in the optic nerves. The large scale degeneration of nerve fibers of the left optic nerve could be traced through the chiasm and into the optic tracts.

**Optic Tracts** Both optic tracts showed demyelination chiefly in the margin, as the result of ascending degeneration. The left optic tract revealed this marginal degeneration all around the tract, while the right optic tract showed marginal degeneration only along the lateral side. In the meninges of both optic tracts was slight plasma cell infiltration, and in the interior of the tracts an occasional round cell could be noted in the vascular sheaths.

**Geniculate Bodies** The ganglion cells were well preserved. There was slight perivascular infiltration of the vessels.

**Base of Brain** In the pia of the floor of the third ventricle, i.e., immediately behind the optic chiasm, there was a slight inflammatory exudate.

**Optochiasmatic Arachnoid** The slightly thickened arachnoid passed innocuously over both optic nerves without being adherent to either of them (fig 1). There was no sign that the optochiasmatic arachnoid had constricted the left, atrophied, optic nerve. Only a few isolated round cells were noted in the arachnoid in this region.

Spirochetes were not observed in the visual pathways, but such organisms were demonstrated in the gray matter of the brain, which revealed the characteristic histopathologic picture of dementia paralytica.

In the spinal cord were no tabetic changes.

*Comment*—The anatomic evidence, which could be pieced together from serial sections, pointed to the intracranial portion of the optic nerves as the starting point of the disease process. The syphilitic exudate in the interior of the nerves had reached its greatest intensity in the demyelinated portion of the left, atrophied, optic nerve. However, a similar, but less intense, inflammatory process was already present in the intracranial portion of the not yet demyelinated right optic nerve. One can safely assume that the exudative process in the already demyelinated left optic nerve has preceded, possibly by several years, the appearance of the syphilitic exudate in the interior of the other, not yet atrophied, nerve. Demyelination of nerve fibers in primary syphilitic optic nerve atrophy is, as a rule, an exceedingly slow process, being the result of a mild, but persistent, inflammation.

*CASE 2—Unilateral syphilitic primary optic nerve atrophy in a patient with meningovascular syphilis*

A policeman at the age of 53 had onset of meningovascular syphilis with mental symptoms. There was a history of chancre twenty years before, with no subsequent treatment. The patellar reflex was slightly exaggerated on both sides. Vision was 20/40 in the right eye. The left eye, at the time of his admission, had been

blind about one year. Perimetric examination of the right eye was unsatisfactory, owing to the disturbed mental state of the patient.

The Wassermann and Kahn reactions of the blood and the Wassermann reaction of the spinal fluid were positive. The Ross-Jones and Pandy tests gave a 4 plus reaction. The total protein was 156 mg per hundred cubic centimeters. The cell count was 103 per cubic millimeter. The colloidal gold curve was 1234221100.

The patient was given a course of tertian malarial therapy. He experienced nine paroxysms of fever, with temperatures ranging from 103 to 105 F. There was no other treatment for syphilis. The patient showed some clinical improvement, but the spinal fluid remained practically unchanged. Even the cell count was uninfluenced by the course of therapeutic malaria, being 88 cells per cubic millimeter shortly before death.

*Postmortem Observations*—Over the pons the arachnoid revealed chronic thickening, but in the optochiasmatic region it had a fairly normal appearance.

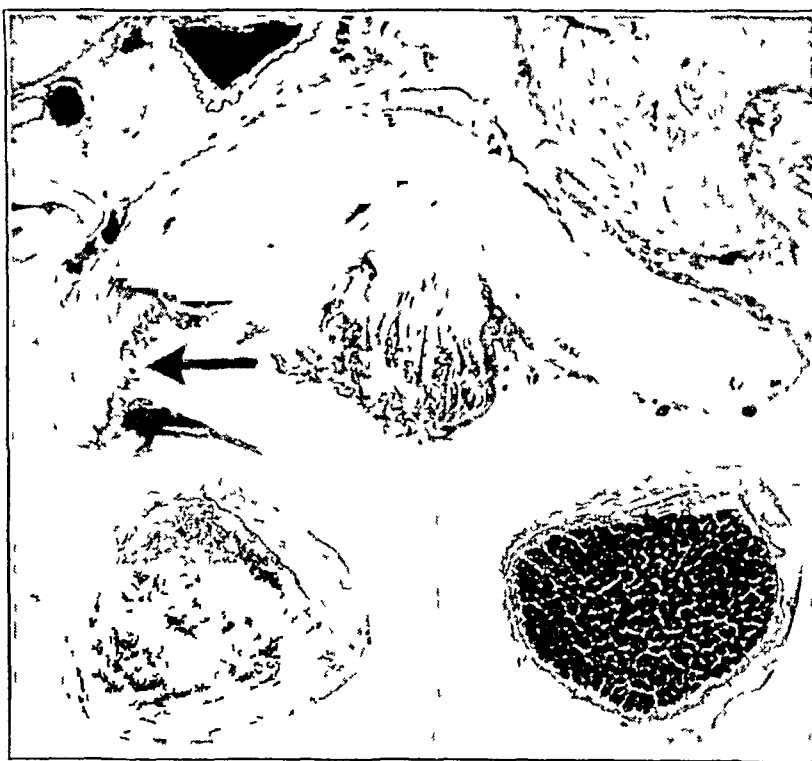


Fig 2 (case 2)—Unilateral syphilitic primary atrophy of the optic nerve in a patient with meningovascular syphilis. The upper picture represents the optic chiasm. There is complete demyelination of the left lateral portion of the chiasm (arrow), where the left optic nerve emerges. In this region the inflammatory process has reached its greatest intensity. See figures 3 and 4.

Below is shown the orbital portions of the left (demyelinated) and the right (normal) optic nerve. Weil's stain for myelin sheaths.

Grossly, there was no indication of severe syphilitic basilar meningitis, as was later revealed by microscopic examination (figs 3 and 4). Strikingly, the optic nerves were almost of the same volume, i.e., the atrophy of the left optic nerve was barely noticeable on gross examination. Over the temporal and lateral regions of the brain there was slight generalized meningeal turbidity, diminishing in intensity toward the upper aspect of the brain. In the left temporoparietal region several cortical infarctions occurred, as the result of syphilitic obliterating endarteritis.

There was beginning syphilitic aneurysm of the arch of the aorta.



*Histologic Examination*—At the base of the brain, but particularly in the optochiasmatic region (figs 3 and 4) there was much exudate (syphilitic basilar meningitis). On the other hand, the meninges of the upper aspect of the brain were free of inflammatory cellular elements. Numerous small and middle-sized vessels at the base of the brain revealed syphilitic panarteritis (fig 4). There were no perivascular round cell infiltrations in the cortex of the brain. The microscopic diagnosis was meningovascular syphilis.

*Optic Pathways* In serial sections it was observed that the most pronounced inflammatory reaction anywhere in the brain was situated in the anterior portion of the chiasm where the left optic nerve made its exit (figs 3 and 4). Here, heavy round cell infiltrations, composed almost exclusively of lymphocytes, penetrated from the margin into the interior of the chiasm, flooding the nerve fibers and producing complete demyelination (fig 2). A most careful and time-consuming



Fig 3 (case 2)—Left lateral demyelinated portion of the optic chiasm. Syphilitic exudate is seen along the margin, penetrating into the interior of the chiasm. Toluidine blue stain.

search for spirochetes in this most infiltrated area, as well as in other parts of the optic pathways and in the brain, did not reveal *Treponema pallidum*. Throughout the remaining cross section of the chiasm there was also a diffuse inflammatory exudate, but obvious demyelination was still absent except in the margin of the chiasm. In the pia of the intracranial portion of both optic nerves there was moderate round cell infiltration, being slightly more pronounced in the atrophied than in the normal optic nerve. In the interior of the intracranial portion of the atrophied optic nerve there were lymphocytes and plasma cells, and the vessels were surrounded by a coat of similar cells. In the intraforaminal region the syphilitic exudate, both in the pia and in the interior, became less intense, and in the midorbital region was almost absent. In the margin, and less so throughout the diameter, of the intracranial portion of the right, normal, optic nerve there was

also round cell infiltration. But, except for the margin, this optic nerve did not show obvious signs of demyelination. In the midorbital portion of this nerve there was no longer any inflammatory reaction, either in the pia or in the interior. This was in contrast to the left, atrophied, optic nerve, where at the same level a few plasma cells could still be observed within the nerve.

In the pia of both optic tracts there was moderate round cell infiltration, and within the tracts occasional plasma cells could be observed.

In the geniculate bodies there were no changes.

*Comment*—In this patient with meningovascular syphilis and unilateral atrophy of the optic nerve, the syphilitic meningitis was almost exclusively confined to the base of the brain. The meningitic exudate



Fig 4 (case 2) —Syphilitic basilar meningitis. Masses of lymphocytes and blood vessels indicate syphilitic endarteritis in the region where the left optic nerve makes its exit from the chiasm. Toluidine blue stain.

had reached its height over the left side of the anterior portion of the chiasm, where the left optic nerve emerges, having produced complete demyelination in this area. Since in most cases unilateral atrophy of the optic nerve becomes bilateral, it was of great interest to ascertain the degree of the inflammatory reaction in the nondemyelinated part of the chiasm and in the right, nonatrophied, optic nerve. In the not yet demyelinated portion of the chiasm and in the still normal optic nerve there was already at this stage enough syphilitic exudate to have led to

demyelination of the nerve fibers in the near future. A great deal has been written on the direct noxious action of spirochetes on the nerve fibers in optic nerve atrophy. For this reason, a most intensive search for spirochetes was made in the optic pathways and in other regions of the brain, but none were found.

From a therapeutic point of view, a most important question arose. A course of induced malaria had failed to reduce the increased cell count of the spinal fluid. In other words, the inflammatory process in the meninges had remained unaltered. It has since been shown that in such instances the subsequent use of 5,000,000 units of penicillin, given by the intramuscular route, will restore the cell count to normal. The therapeutic implication of this observation in the treatment of syphilitic optic nerve atrophy is clear. In its management one should not rely on induced malaria alone, or on penicillin alone. For the best possible effect on the underlying inflammatory process, malaria therapy and the simultaneous administration of 5,000,000 to 7,000,000 penicillin units, followed immediately by another course of 5,000,000 units, should be advocated. This suggestion<sup>2</sup> has already found adherence in one of the most progressive centers for treatment of syphilis.<sup>3</sup>

#### GENERAL COMMENTS

In by far the largest majority of cases of syphilitic primary optic nerve atrophy, both optic nerves are affected simultaneously, but frequently the process is more advanced on one side than on the other. In only 10 of 250 cases of the Johns Hopkins material was the atrophy of the optic nerve unilateral at the time of the initial examination.<sup>4</sup>

Histologic study in the 2 cases of unilateral syphilitic atrophy of the optic nerve has shown clearly why, with few exceptions, unilateral optic nerve atrophy is almost always followed by bilateral involvement. In both cases, at the time of death, there was present in the not yet demyelinated optic nerve an exudative process which was considered sufficient to bring about demyelination in due time.

Involvement of the unaffected nerve may in occasional patients be very slow. Moore and associates<sup>4</sup> observed 5 patients with unilateral optic nerve atrophy who maintained normal visual acuity in the unaffected eye for three or more years without treatment. In a rare case the process may remain monocular for as long as six to twelve years.<sup>4</sup> In such an

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2 Bruetsch, W. L. Malaria Therapy in Syphilitic Primary Optic Atrophy, *J. A. M. A.* **130** 14 (Jan 5) 1946.

3 Moore, J. E. Penicillin in Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1946, pp. 200 and 273.

4 Moore, J. E., Hahn, R. D., Woods, A. C., and Sloan, L. The Treatment of Syphilitic Primary Optic Atrophy, *Am. J. Syph., Gonorr. & Ven. Dis.* **26** 407, 1942.

instance the inflammatory process is apparently strictly limited to the intracranial portion of one optic nerve. Such a case was studied by Richter,<sup>5</sup> who observed, on histologic examination, one optic nerve with normal nerve fibers and no round cell infiltration in the pia or in the interior of the nerve. The other optic nerve was atrophied. In this nerve there was a large amount of exudate in the pia and in the septums. The chiasm and optic tracts were free of an inflammatory process. This instance is an excellent example of the theory<sup>6</sup> that demyelination in primary syphilitic optic nerve atrophy is dependent on inflammation.

A few words should be said as to the role of the optochiasmatic arachnoid in the causation of optic nerve atrophy. Of late, the theory has been advanced that syphilitic arachnoiditis involving the optic nerves is responsible for the atrophy of the optic nerves.<sup>7</sup> In neither of the 2 cases with unilateral atrophy of the optic nerve was there pronounced thickening of the arachnoid in the optochiasmatic region, nor was there any evidence of mechanical constriction about the atrophied optic nerves. In an extensive anatomic study of primary syphilitic optic nerve atrophy I<sup>8</sup> have definitely disproved this theory. In 5 of 10 cases of complete syphilitic optic nerve atrophy of my material there were no arachnoidal adhesions at all in the optochiasmatic region. In the other instances there was syphilitic arachnoiditis, but the arachnoidal thickening was merely an incidental change, and could not be connected with the atrophy of the optic nerves.

#### CONCLUSIONS

Unilateral syphilitic primary atrophy of the optic nerve is almost always the forerunner of bilateral atrophy of this nerve. At the time the demyelination of the nerve fibers has progressed to complete degeneration in one optic nerve, there is already present in the normal nerve a syphilitic inflammatory exudate which ultimately will lead to atrophy of the not yet demyelinated optic nerve.

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5 Richter, H. Zur Histogenese der Tabes, *Ztschr f d ges Neurol u Psychiat* **67**:1, 1921.

6 Bruetsch, W. L. The Pathogenesis and Pathology of Syphilitic Primary Optic Atrophy, *Am J Syph, Gonorr & Ven Dis*, to be published.

7 Vincent, C., Jeandelize, and Bretagne. Atrophie optique tabetique et neuro-chirurgie, *Bull Soc d'ophth de Paris* **49** 245, 1937. Vail, D. Syphilitic Opticochiasmatic Arachnoiditis, *Tr Am Ophth Soc* **36**:126, 1938. Hausman, L. The Surgical Treatment of Syphilitic Optic Atrophy Due to Chiasmal Arachnoiditis, *Am J Ophth* **24** 119, 1941. Schaub, C. F. Surgical Treatment of Syphilitic Optic Atrophy (Syphilitic Optico-Chiasmatic Arachnoiditis), *Dis Eye, Ear Nose & Throat* **1** 326, 1941.

8 Bruetsch, W. L. Surgical Treatment of Syphilitic Primary Optic Atrophy (Syphilitic Optochiasmatic Arachnoiditis), *Tr Am Neurol A* **71**:129, 1946, Surgical Treatment of Syphilitic Primary Optic Nerve Atrophy (Syphilitic Optochiasmatic Arachnoiditis), *Arch Ophth* **38**:735 (Dec) 1947, The Etiology of Optochiasmatic Arachnoiditis, *Arch Neurol & Psychiat*, to be published.

Syphilitic optochiasmatic achnoiditis, which is frequently present in neurosyphilis, has nothing to do with the causation of the atrophy of the optic nerves

The most efficacious treatment of syphilitic optic nerve atrophy is malarial therapy, aided by concomitant and subsequent courses of penicillin, each course consisting of administration of at least 5,000,000 units

#### ABSTRACT OF DISCUSSION

DR C S O'BRIEN, Iowa City The atrophy of the optic nerve associated with untreated neurosyphilis is almost invariably bilateral. Although degenerative changes in one nerve may manifest themselves clinically long before apparent involvement of the other nerve, one must never base an opinion of atrophy of the optic nerve on ophthalmoscopic studies alone, inasmuch as early degenerative changes are not visible and therefore early diagnosis must be made on defects in the visual fields. The pathologic observations in each case described by Dr Bruetsch establish the fact that both nerves were involved even though he entitled his paper "Unilateral Syphilitic Primary Optic Atrophy." It is probable that had it been possible to make satisfactory studies of the visual fields on the better eye of each patient, the patient with dementia paralytica would have shown concentric contraction with a sector defect in the field, since pathologic studies revealed inflammation and beginning peripheral demyelination with extension in one area into the interior of the nerve. The patient with meningovascular syphilis would have had some concentric contraction of the visual field, since microscopically the nerve showed marginal demyelination.

The pathogenesis of syphilitic primary atrophy of the optic nerve is still a moot point. This is due to the fact that almost never has it been possible to demonstrate *Treponema pallidum* either in the leptomeninges surrounding the nerve or in the nerve itself. A definite toxin may be present, but its presence has not yet been proved. Some believe that the degeneration of the nerve is secondary to vascular lesions, with resultant lack of nutrition. Others have postulated a combination of syphilitic disease and vitamin B deficiency. Still other theories have been propounded. All such explanations seem unnecessary, since the degeneration of the nerve fibers may be accounted for on the basis of chronic leptomeningitis and interstitial neuritis. Such being the case, the optic nerve atrophy of neurosyphilis is not in reality primary, but is a secondary type, due to peripheral and interstitial neuritis, beginning usually in the intracranial portion of the nerve and manifesting itself on ophthalmoscopic examination as a primary atrophy only by reason of a descending degeneration without visible inflammatory changes in the nerve head.

In all types of neurosyphilis the pathologic process of optic nerve atrophy is essentially the same, i. e., a peripheral and an interstitial inflammation, followed by gliosis with demyelination and degeneration of the nerve fibers. Moore and Woods<sup>4</sup> expressed the belief that pathologic changes in the optic nerves begin in the intracranial portion just anterior to the chiasm as leptomeningitis and interstitial neuritis and that degenerative changes appear first in the marginal nerve fibers.

This is demonstrated in the 2 cases under discussion. Dr Bruetsch stated<sup>2</sup> that his findings in 70 cases of neurosyphilis confirmed the conclusions reached by others before him, namely, that in the optic nerve atrophy of tabes, dementia paralytica, the tabetic form of dementia paralytica and meningovascular syphilis there are a chronic, low grade inflammatory process in the pia-arachnoid surrounding the nerve and a similar process in the nerve septums, followed by demyelination and atrophy of the nerve fibers and secondary gliosis. In dementia paralytica and in meningovascular syphilis, the meninges and brain in the region of the anterior pole are affected more severely than in other areas; hence, as one would expect, the chiasm and the intracranial portion of the optic nerves are usually involved more than the orbital portion of the nerves. In the 2 cases reported here the pathologic changes are therefore typical. Indicative of the chronic, sluggish nature of the inflammation are the perivascular round cell infiltrations, composed of lymphocytes and plasma cells, in the pia-arachnoid and nerve septums.

Dr Bruetsch seems to be convinced that optochiasmatic arachnoiditis need not be considered as a cause of syphilitic atrophy of the optic nerve. However, it is believed that further study is necessary before one can be sure that it may not be the etiologic factor in an occasional case of atrophy of the optic nerve.

The modern treatment of syphilitic optic nerve atrophy is based on the belief that inflammatory changes precede, and are responsible for, degeneration of the nerve fibers. Malaria and penicillin are effective agents against syphilitic inflammation, and, while they will not restore degenerated nerve fibers, they will prevent additional damage after control of the inflammatory process. The fact that this form of therapy arrests the progress of the atrophy lends support to the theory that degeneration of the nerve fibers is due to peripheral and interstitial neuritis.

DR JOSEPH V. KLAUDER, Philadelphia. I am sure all appreciate Dr Bruetsch's excellent and painstaking studies. Aided by improved methods of staining, enthusiasm and, above all, skill, he has gone further in pathologic studies of optic nerve atrophy than has any other investigator.

Dr Bruetsch's thesis is that syphilitic primary atrophy of the optic nerves is an inflammatory process. The starting point of such a process is the intracranial portion of the nerves. Inflammatory symptoms are conspicuous around the chiasm and were present around both nerves in the 2 cases he studied, although only one nerve showed demyelination. In the histopathologic concept, therefore, the atrophy was bilateral. It was unilateral only in the clinical concept. The inflammatory process is at first extraneural and later becomes intraneural, preceding demyelination of the nerve.

Dr Bruetsch's studies have interesting clinical correlations. He demonstrated in 1 case that inflammatory processes invading the nerve prior to demyelination caused constriction of the visual fields. Improvement in the degree of constriction followed treatment. Heretofore, one questioned such an occurrence, in the belief that degenerated nerve fibers cannot be restored. The answer is that in such cases the optic nerve is not atrophied or demyelinated.

The author observed optochiasmatic arachnoiditis, in none of his cases, however, was it of sufficient degree that cicatricial bands constricted the optic nerves. His studies bring into question this alleged cause of atrophy of the optic nerve and therefore challenge the justification of surgical procedures in treatment.

It would be of interest to know the duration of the stage of optic nerve atrophy recognizable by objective evidence—the ophthalmoscopic findings and perimetric fields—which precedes the subjective symptom of impaired visual acuity. My clinical impression is that the duration of this stage varies from a few months to as long as several years and that in 5 per cent of all cases of neurosyphilis or acquired syphilis of more than ten years' duration the optic nerve atrophy can be diagnosed in the stage of presubjective symptoms.

Unilateral atrophy of the optic nerve is rarely seen among the clinic patients at Wills Hospital. The reason becomes obvious in considering the data compiled by Lehrfeld and Gross (*Am J Ophth* 21: 435, 1938) on 600 patients with primary optic nerve atrophy of syphilitic origin at Wills Hospital. At the onset of impaired visual acuity 31 per cent of these patients consulted an optometrist as an initial means of treatment. An average of eighteen months elapsed between the onset of impaired vision and proper treatment. When first seen at the clinic, 64 per cent had visual acuity of 6/24 or less and 19 per cent had visual acuity of 6/60 or less.

This is our unfortunate experience in the early diagnosis of optic nerve atrophy at this clinic. Apparently the optometrist sees one-third more patients with early atrophy of the optic nerve than does the ophthalmologist. I could make a point of this observation in favor of having the optometrist trained to recognize papillary abnormalities as indicative of syphilitic optic nerve atrophy and refer such patients for proper study and treatment. It intimately concerns the discussion I have just heard concerning the teaching of optometrists by ophthalmologists.

There are important clinical implications in Dr. Bruetsch's studies. The vital importance of syphilitic optic nerve atrophy needs no emphasis. The 10 to 15 per cent of all blindness caused by syphilis (essentially optic nerve atrophy) approaches the incidence of blindness caused by cataract and glaucoma. Syphilis as a cause of blindness is deserving of as much attention as is now being given to glaucoma. I appeal to ophthalmologists for more interest in syphilis as a systemic disease, its public health aspects and its treatment.

The importance of early diagnosis and the need of antisyphilitic treatment, especially fever and penicillin, are clinical correlations of Dr. Bruetsch's studies. Undue pessimism that optic nerve atrophy always pursues an unfavorable course after treatment is not justified.

To facilitate early diagnosis, it is necessary that ophthalmologists and all physicians who examine syphilitic patients have a high degree of awareness of atrophy of the optic nerves, especially the tabetic type. Routine ophthalmologic examination should be conducted on all patients with neurosyphilis. In records of private, ward and clinic patients too frequently no mention is made of the status of the optic nerve unless the patient complains of impaired visual acuity. Especially in all clinics for syphilitic patients ophthalmologic examination should be facilitated.

Dr. Bruetsch's emphasis on use of fever and penicillin in treatment will, I am sure, find general agreement. I subscribe to initial treatment with 5,000,000 to 7,000,000 units given conjointly with induction of fever, but am not yet prepared to say in what amount and for how long penicillin should be administered. Further study is necessary to determine this. Frequently it is necessary to individualize treatment.

Results at Wills Hospital with penicillin treatment of optic nerve atrophy have been encouraging. Years of observation, however, will be required to define the status of the drug as a therapeutic agent.

DR. WALTER L. BRUETSCH, Indianapolis. I should like to stress one point. Penicillin should be given as long as there is a trace of vision left. There is always the hope that the process may be arrested before the light goes out entirely.



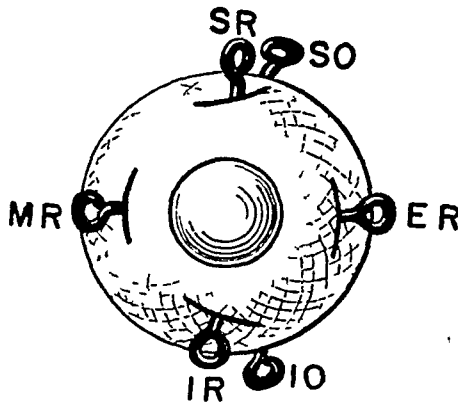
# Clinical Notes

## STUDENTS' MODEL FOR DEMONSTRATION OF ACTION OF THE EXTRAOCULAR MUSCLES

DAVID G COGAN, M D  
BOSTON

The varying action of the individual extraocular muscles in different positions of the eyes is often confusing to the student, and little enlightenment is to be found in texts, which categorically divide the actions into "primary" and "secondary," leaving the student to memorize the functions by rote

Believing that a simple mechanical device may give the student a functional interpretation of the changing action, I have for the past several years had students make a golf ball model, which in its simplicity, cost and ease of construction has distinct advantages over the ophthalmotropes frequently used. It is described here in the belief that it may have some general usefulness in postgraduate teaching



Golf ball model of the left eye

A standard golf ball is just twice the size of the normal adult eye, and some standard furniture gliders are twice the size of the cornea. The glider prongs are hammered into the golf ball, and the insertions of the muscles are indicated with india ink on the globe (figure) at appropriate distances from the "limbus," according to the diagrams and measurements (doubled) given in Whitnall's text<sup>1</sup>. A screw eye is then placed at the midpoint of the insertion of each muscle.

To illustrate the action of any one muscle, a piece of string is attached to the corresponding screw eye, the golf ball is held between the thumb

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<sup>1</sup> Whitnall, S E. The Anatomy of the Human Orbit and Accessory Organs of Vision, ed 2, New York, Oxford University Press, 1932

and finger of one hand with the "cornea" facing in any desired direction, and the unattached end of the string is held with the other hand in the position from which the pull of that muscle is normally exerted on the globe. Traction on the string will then exert a pull corresponding to the normal action of the particular muscle. After a relatively few manipulations of the model, the student finds he can visualize the function of each muscle in various positions of the eye, without having to depend on an all too fickle, and often treacherous, memory.

The model here described illustrates the actions of the muscles for one eye only. Conjugate movements may be simulated by making a model for each eye separately. This, however, is usually unnecessary, since the changing action of the extraocular muscles learned on the one eye for different positions of gaze may be readily applied to that for conjugate movements.

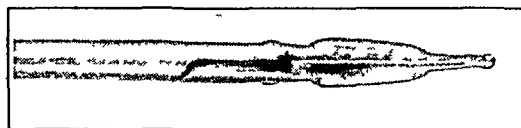
243 Charles Street

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### GUARDED MUSCLE SCISSORS

JESSE M. LEVITT, M.D.,  
BROOKLYN

To eliminate the possibility of cutting into the eyeball in surgical procedures on the extraocular muscles, guards were placed on a pair of Aebli muscle scissors. The points of the scissors were blunted with small spherical knobs. Elevator guards, 0.8 mm high, 9.5 mm long and 2.5 mm wide, were placed on both blades halfway between the ball tips and the screw, as shown in the accompanying figure<sup>1</sup>. With the increasing amount of surgical work on the oblique muscles now being done, these guards add a special factor of safety. They are particularly useful in operations on the inferior oblique muscle, in which



Guarded muscle scissors

there is danger of injury to the long ciliary nerve, the vortex veins and the macular area.

These scissors have proved useful in other ways. A uniform stump is left in muscle resections when the scissors are applied flush with the sclera. Sutures can be tied close when held taut without cutting the knots when the scissors are applied flush with the united muscle. The scissors have also been found helpful in enlargement of cataract incisions, affording easy entrance into the anterior chamber and limiting the extent to which the blade can be introduced.

991 Ocean Avenue (26)

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<sup>1</sup> The instrument was made by V. Mueller & Co., Chicago

# News and Notes

EDITED BY DR W L BENEDICT

## GENERAL NEWS

**Leslie Dana Award**—The National Society for the Prevention of Blindness, Inc, is pleased to announce that the Leslie Dana Gold Medal, awarded annually for outstanding achievements in the prevention of blindness and the conservation of vision, was presented to Dr Frederick H Verhoeff, of Boston. The medal was presented by Dr Lawrence T Post, of St Louis, during the faculty luncheon of the American Academy of Ophthalmology and Otolaryngology, in Chicago, on Thursday, October 16. Dr Verhoeff was selected for this honor by the St Louis Society for the Blind, through which the medal is offered by Mr Leslie Dana, of St Louis. This highly prized token of recognition in the field of public health is given on the recommendation of the Association for Research in Ophthalmology, Inc.

**Glaucoma Prize Offered by the International Association for Prevention of Blindness**—The office of the International Association for Prevention of Blindness announces an honorarium of \$1,000 to promote research in ophthalmology is offered through the American members of the International Association, the judges to consist of the executive committee, the president and the officers of the association. The award will be made in connection with the Sixteenth Concilium Ophthalmologicum. Papers may be presented by any responsible research worker. The subject is "Simple Noninflammatory Glaucoma" and may include anything definitely related to the problem. The matter must be new and of such value, in the judgment of the jury, as to merit this recognition. Papers may be written in English or French, and they should be those heretofore unpublished or those published between the date of this announcement and Oct 15, 1949. They should be in the hands of the secretary of the International Association for the Prevention of Blindness, 66 Boulevard Saint-Michel, Paris, through whom they will be sent to the members of the judicial committee, not later than Oct 15, 1949. The decision of the judges will be final.

**Schoenberg Memorial Award Lecture**—Dr Peter C Kronfeld, chief of the ophthalmic service of the Illinois Eye and Ear Infirmary, gave the first Mark J Schoenberg Memorial Award lecture on Monday evening, Dec 1, 1947, at the New York Academy of Medicine. His subject was "The Canal of Schlemm." Members of the committee to choose a lecturer each year in honor of the late Dr Schoenberg are Isadore Givner, M D, chairman, John N Evans, M D, Willis S Knighton, M D, Adolph Posner, M D, and James W Smith, M D.

**American Academy of Ophthalmology and Otolaryngology**—The annual meeting in 1948 will be held at the Palmer House, in Chicago, on October 10 to 15.

The Council for 1948 consists of the following officers: Carl H McCaskey, M D, Indianapolis, president, Conrad Berens, M D, New

York, president-elect, Ralph O Rychener, M D , Memphis, Tenn , first vice president , Rea Ashley, M D , San Francisco, second vice president ; Ray K Daily, M D , Houston, Texas, third vice president , Lawrence T Post, M D , St Louis, past president , Gordon B New, M D , Rochester, Minn , past president , Alan C Woods, M D , Baltimore, past president , William L Benedict, M D , Rochester, Minn , executive secretary-treasurer, editor and business manager of the *Transactions* , Algernon B Reese, M D , New York, secretary for ophthalmology , James H Maxwell, M D , Ann Arbor, Mich , secretary for otolaryngology , A D Ruedemann, M D , Detroit, secretary for instruction in ophthalmology , Dean M Lierle, M D , Iowa City, secretary for instruction in otolaryngology and maxillofacial surgery , Lawrence R Boies, M D , Minneapolis, secretary for home study courses , Erling W Hansen, M D , Minneapolis, secretary for public relations , James M Robb, M D , Detroit, councillor , C D Blassingame, M D , Memphis, Tenn , councillor , Thomas D Allen, M D , Chicago, councillor , Fletcher D Woodward, M D , Charlottesville, Va , councillor

**Dr. E. V. L. Brown to Lecture at Joint Meeting of Institute of Medicine of Chicago, Chicago Ophthalmological Society and Society of Medical History of Chicago.**—The Institute of Medicine of Chicago announces that Dr E V L Brown, Rush Clinical Professor Emeritus in ophthalmology, University of Illinois College of Medicine, delivered the first presentation under the gift of the Rudolph Wieser Holmes and Maria Baxter Holmes Fund, in memorial to Edward Lorenzo Holmes, at the Palmer House on Friday evening, January 30, at a joint meeting with the Chicago Ophthalmological Society and the Society of Medical History of Chicago His subject was "Edward L Holmes Pioneer Chicago Eye Doctor "

#### SOCIETY NEWS

**New York Association for the Blind.**—The New York Association for the Blind, 111 East Fifty-Ninth Street, New York 22, has sent the following program to ophthalmologists, medical workers and welfare agencies

"For the person who is losing his sight, or who has just lost it, the knowledge that he can be trained to read and to write Braille, to work, to receive understanding guidance, and to enjoy himself through recreation and play, may change his whole outlook from despair to hope from hope to realization

"All of our services are free to the blind of all ages, races, and creeds, rich as well as poor, who are residents of Manhattan, Bronx, Queens and Richmond Through training for selective placement, many persons without sight have demonstrated their ability to be successful in industry and have become self-supporting

"We are especially interested in blind infants and children of preschool age, who are visited and supervised in their homes by our experienced medical social workers until they are ready for our Light-house Nursery School

"We hope you will bring to our attention any totally blind child or adult or any individual with seriously defective vision, to whom we may offer our many services—Marian Held, Director, Department of Direct Services "

**Annual Congress of the Ophthalmological Society of the United Kingdom**—The annual congress of the Ophthalmological Society of the United Kingdom will be held at the Royal Society of Medicine, 1 Wimpole Street, London, W 1, on Friday and Saturday, April 9 to 10, 1948

The subject for discussion will be subjective disorders of vision, exclusive of those due to local ocular disease. The discussion will be opened by Dr Macdonald Critchley, Prof Henry Cohen and Mr J H. Doggart

On this occasion the Bowman Lecture will be delivered by Prof. Marc Amsler, Zurich, Switzerland

On Friday afternoon there will be a joint clinical meeting with the Ophthalmological Section of the Royal Society of Medicine at the Ophthalmic Institute, Central London Ophthalmic Hospital, Judd Street, London, W C 1

The annual dinner will be held at the Royal College of Surgeons on Thursday, April 8

Honorary secretaries are E F King (council business) and T Keith Lyle (congress business)

**Back Volumes of Transactions of the Ophthalmological Society of the United Kingdom**—The Ophthalmological Society of the United Kingdom holds a considerable stock of certain volumes of the *Transactions* since their first edition. The volumes for the following years however, are not available: 1897, 1898, 1899, 1900; 1901, 1902, 1905, 1906, 1907, 1908, 1909, 1911, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1926, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935 and 1937 (part 1)

The council feels that many libraries, both at home and abroad, may wish to complete their sets and will be glad to present to libraries, medical schools and hospitals such available volumes as they may desire. No charge will be made other than the cost of postage.

Those interested are asked to communicate with the Bowman Librarian, Royal Society of Medicine, 1 Wimpole Street, London, W 1

**Ophthalmological Society of Egypt**—The annual meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on Friday and Saturday, March 12 and 13, 1948, at 9 a m. Medical practitioners, oculists and others are cordially invited.

**Ophthalmological Society, Guadalajara, Mexico**—An ophthalmological society has been founded in Guadalajara, Mexico. Dr Elias Mendoza Gonzalez is president and Dr L. Nuñez Leal, secretary.

#### PERSONAL NEWS

**Corneal Transplantation Discussed by Dr. A E. Maumenee**—Dr. A E Maumenee recently discussed "Corneal Transplantation" for the members of the department of ophthalmology of the University of Alabama School of Medicine, at the Thigpen-Cater Eye Hospital.

# Correspondence

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## CORRELATIONS BETWEEN SENSORY AND MOTOR DISTURBANCES IN CONVERGENT SQUINT

*To the Editor* —The paper by Dr Francis Heed Adler and F Elizabeth Jackson published under this title in the September 1947 issue of the ARCHIVES is, in my opinion, an important step toward the clarification of the problem of retinal correspondence in squint. The data contained in the paper were derived from a large number of uniformly observed cases, and as to their validity there can be no question. Still, with the authors' tabulation and interpretation of their data at least one reader cannot fully agree.

In analyzing their cases, Adler and Jackson found that out of 175 cases of squint, normal correspondence was present in 64, or 35 per cent. The remaining 111 cases are tabulated under the heading "anomalous correspondence." This is regrettable, since to the superficial or uninitiated reader it will convey the impression that the authors' data confirm the belief that anomalous correspondence is a common, typical, and therefore important, attribute of established comitant squint. In fact, they prove just the opposite.

The subdivision of the cases tabulated under "anomalous correspondence" into several types shows that in only 5 out of a total of 111 cases was there what is called "harmonious anomalous correspondence," the only type for which even the most ardent adherent of an empiricist theory of binocular correspondence could claim any purposiveness. Another 17 cases were labeled as "unharmonious." The overwhelming majority of the cases of squint tabulated under the heading "anomalous correspondence," viz., 89 out of 111, are described in the text as cases "without functional correspondence, since no particular area is found to correspond directionally with the fixing macula."

A clearcut statement from such an eminent source, based on such irrefutable evidence as the authors have to offer, would have helped many a befuddled reader to make it finally clear to himself that even the vestige of a sensorial relationship between the two eyes' (i.e., a directional relationship) is exceptional in cases without normal binocular correspondence. The tabulating of cases "without functional correspondence" under the general heading "anomalous correspondence," as the authors found it fit to do, will only confuse him more.

I realize that this is not the opportunity to unfold the whole question of so-called anomalous correspondence. While the discovery of an anomalous directional relationship between a squinter's eyes seemed to be a welcome piece of evidence for the adherents of a bygone empiricism, today few will accept Duke-Elder's statement that secondary correspondence, as he calls it, "may be capable of eliciting full stereoscopic vision." A number of authors, of whom probably Travers is the best known, have shown that actually an area of suppression is found in that region of the squinting retina which adherents of the empiricist theory adorned with the misleading term "false macula." The fact that

persons with transient exotropia have normal correspondence and good binocular vision while their eyes are straight but report an anomalous directional relationship whenever one eye is turned indicates that the latter is a musculosensory phenomenon rather than one of adaptation or a sign of any kind of binocular vision

The conclusion that one certainly is justified in drawing from the data published in this paper should, in my opinion, be formulated as follows

1 Persons with squint who have no normal correspondence only exceptionally show any anomalous binocular directional relationship (which may be adapted or not adapted to the angle of squint)

2 Their overwhelming majority is "without functional correspondence" whatever

ARTHUR LINKSZ, M D , New York

6 East Seventy-Sixth Street (21)

*To the Editor* —Dr Linksz is quite correct in stating that we have tabulated 80 per cent of the patients who did not have normal correspondence but who had suppression under the heading of "anomalous correspondence" We are in agreement with Dr Linksz that this is an unfortunate term to use for this group, but no better one has been agreed on and the subject is still extremely controversial Lancaster, Harms, Travers and Burian all classify this group of patients with those in whom anomalous correspondence can be proved with the major amblyoscope Swan, Linksz and others object to the definition of "anomalous correspondence" as a condition in which the fovea of one retina and an eccentric element of the other acquire a common visual direction, since such a functional relation can be demonstrated in so few patients with anomalous retinal correspondence

In the 80 per cent of patients with suppression, there is no functionally corresponding point in the squinting eye with the fovea of the fixing eye Unfortunately, one cannot say that these patients have no functional correspondence whatever, since Burian states that in virtually every case it can be shown with the double image test that such a relationship does exist One can only be certain that this group of patients does not have normal correspondence It seems to me best that they be retained in the group with so-called anomalous correspondence until some final agreement among our experts is attained

FRANCIS HEED ADLER, M D , Philadelphia

Hospital of the University of Pennsylvania

## Obituaries

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### LOUIS STORROW GREENE, M D

1872-1947

Louis Greene was born at Columbus, Ga , on Nov 19, 1872, the youngest son of Col William Spencer Greene and Anne Storrow Greene After obtaining his early education in schools in Alabama and Virginia, he received the degree of Doctor of Medicine from the



LOUIS STORROW GREENE, M D

1872-1947

University of Virginia in 1895 and then acted as intern in the Charity Hospital, New York city In 1897 he entered on the practice of ophthalmology in Washington, D C , and was associated with the late Dr William H Wilmer for a number of years He continued in active practice in Washington until his death, on Nov 12, 1947



Dr Greene was one of the original members of the staff of the Episcopal Eye, Ear and Throat Hospital when it opened on April 8, 1897 and had acted as chief of the ophthalmic service for the past twenty years, where his ability as an organizer and his interest in clinical ophthalmology were outstanding

He became a member of the American Ophthalmological Society in 1908 and was a faithful and regular attendant at all the meetings serving on the council and becoming president in 1936 He was a member of the Washington, D C, Ophthalmological Society and of the French Ophthalmological Society and was made a life member of the Medical Society of the District of Columbia in 1943 During World War I he was ophthalmologist to the National Medical Advisory Board and was chief of the District of Columbia's eye-examining service for draftees

Dr Greene married Louise Packword Burke on Jan 7, 1903, a son, Julian Burke Greene, and a daughter, Ann Carter Greene, with Mrs Greene, survive

Lou Greene was a man of sterling qualities, and under a somewhat reticent exterior was hidden a kindly and strong personality He was devoted to his work, to his family and to his host of friends, as he went quietly along his way, doing good wherever he was It can truly be said of him that he was a gentleman of the old school His genial smile, dry wit and wise counsel will remain as cherished memories to those of us who were privileged to be counted among his friends

EVERETT L GOAR, M D

## SELIG HECHT, Ph D

1892-1947

All workers in vision will feel a deep sense of loss in the passing of Selig Hecht, who died suddenly on Sept 18, 1947, at the age of 55. Hecht was the outstanding authority of his generation in the physiology of vision. The breadth and significance of his contributions to this field and his unequalled mastery of its literature made him for many years its recognized spokesman.

Selig Hecht was born in Glogow, Austria, on Feb 8, 1892. He was brought to this country as a child and was educated in the public schools of New York City. After obtaining the degree of Bachelor of Science from the College of the City of New York in 1913, he entered Harvard for graduate training in biology. There he undertook research for the doctorate with G. H. Parker and received the degree of Doctor of Philosophy in 1917.

For the next four years Hecht worked as assistant professor of physiology in the Creighton University School of Medicine, Omaha. During this period he laid the foundations of much of his later research. In a series of quantitative studies on the physiology of light responses in the ascidian *Ciona* and the clam *Mya*, Hecht revealed what he concluded to be the essential features of all photoreceptor processes. He showed that these are in all cases constructed about pseudoreversible photochemical systems, in which some photosensitive pigment is destroyed by light and is simultaneously reformed by ordinary chemical reactions. In the breakdown of such a light-sensitive pigment to a steady state concentration Hecht recognized the basis of light adaptation, and in the resynthesis of this pigment in darkness he saw the source of dark adaptation. Hecht also at this time performed his classic experiments on the bleaching of rhodopsin in solution.

From 1921 to 1926, Selig Hecht was a National Research Council fellow in chemistry, working at the universities of Liverpool and Cambridge in England, at the Naples Zoological Station and at the Harvard Medical School. In 1926 he was called to the professorship of biophysics at Columbia University, and this post he retained until his death.

At Columbia Hecht devoted himself primarily to the study of human vision, and here his contribution is the most comprehensive since that of von Helmholtz. In rapid succession, he formulated simple, rational approaches to problems of human dark adaptation, intensity discrimination, visual acuity and the fusion of flickering lights. In 1930 he brought together what had been widely scattered and unorganized data

in a new theory of human color vision, the most original and provocative contribution to the subject in this century

Most recently, Hecht had become interested in quantum relations of vision. In a brilliant analysis a few years ago, he showed that the minimal sensation of light can be excited by the absorption in the retinal rods of only 5 to 7 quanta of radiation. The circumstances



SELIG HECHT, PH D  
1892-1947

surrounding this conclusion made it reasonably certain that a single rod can be stimulated by the absorption of 1 quantum. The consequences of this realization for the theory of vision are incalculable, and Hecht was in the midst of developing them further at the time of his death.

For his work in vision Hecht received the Frederick Ives Medal of the Optical Society of America in 1941. He was elected to mem-

bership in the National Academy of Sciences in 1944. During the war he served on the Subcommittee on Visual Problems of the National Research Council and on the Executive Committee of the Army-Navy Office of Scientific Research and Development Vision Committee. He directed visual research under a number of contracts with the military forces.

Hecht was a brilliant teacher and lecturer. He was selected as a national Sigma Xi lecturer in 1943. His intellectual interests carried his teaching activities far outside the field of vision. He enjoyed greatly giving a series of lecture courses on a variety of scientific subjects at the New School in New York City. His book "Explaining the Atom" (New York, the Viking Press, 1947) is widely recognized as among the best lay approaches to atomic structure and energy. Hecht was also honorary vice president of the Emergency Committee of Atomic Scientists, the only nonatomic scientist in this group.

Such a review as this of Hecht's accomplishments and activities conveys nothing, however, of the essential character of the man. He was one of the most striking and vivid personalities of his time, a man of deep cultivation, broad interests, deft wit and warm sympathy. He was interested in everything, his mind was never at rest. He was an accomplished painter, understood music as do few nonprofessional musicians, read widely and always well and enjoyed intensely everything he did. One could scarcely know him without being changed by the experience. In his death all scientists will recognize the passing of a great scientist, and they, and many others, will feel the loss of a warm friend.

GEORGE WALD

# Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

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## Experimental Pathology

EXPERIMENTAL DINITROPHENOL CATARACT J W BETTMAN, Am J. Ophth 29: 1388 (Nov) 1946

Bettman summarizes his experiments and draws the following conclusions

Dinitrophenol acts on the lenses of mammalian and avian species only in vivo

Lenses in vitro did not form this opacity This difference may be because (a) dinitrophenol, when in the anterior chamber, forms another compound, which then acts on the lens, (b) the permeability of the lens capsule is different when the lens is in vitro than when it is in its normal state, or (c) dinitrophenol interferes with some phase of metabolism of the living lens, for example, causing an increased need for oxygen or producing more lactic acid

The failure of mammals to show the transient lenticular opacities observed in fowl is due to a difference in metabolism of the species, not to a difference in the lenses themselves

The variations due to metabolism are confirmed by the occasional occurrence of permanent cataract in congenitally obese mice Such opacities did not occur in nonobese mice This frequency of cataract formation is comparable to the incidence of cataract in obese human beings and may explain the previous failures of numerous investigations to produce cataracts in experimental mammals

The difference in incidence of cataract in fowl and in mammals is apparently not due to the difference in body temperature The age of the animal is little, if at all, related

W S REESE

EFFECT OF OILY DROPS ON EYES EXPOSED TO MUSTARD VAPOR G I UHDE and E B DUNPHY, Am J Ophth 29: 1562 (Dec) 1946

From experiments on rabbits, Uhde and Dunphy conclude that the current belief in the danger of using oily drops in the treatment of eyes exposed to mustard gas (2-chloroethyl sulfide) vapor is unfounded

W S REESE

## General Diseases

THE MODERN CONCEPT OF THE ADIPOSEGENITAL SYNDROME M ALBEAUX-FERNET and G LOUBLIE, Arch d'opht 6: 257, 1946

This paper is a review of this condition The syndrome is as frequent in one sex as in the other and first manifests itself in childhood or adolescence, rarely in early adult life The characteristics are described, and the diagnosis is reviewed from the point of view of

roentgenologic and ophthalmologic examinations The authors point out that examination of the visual fields is the most important part of the ophthalmologic study and that a common finding is bitemporal hemianopsia, but that sometimes a homonymous hemianopsia may be present. Examination of the pupil is of little value The clinical forms of the syndrome are described In the pure state the condition is due to a chromophobic adenoma of the hypophysis or to a craniopharyngioma The histologic work which has been reported is reviewed The dystrophies are also considered in connection with this syndrome A bibliography of the recent work is appended S B MARLOW

TWO CASES OF RETINITIS IN ACUTE INFECTIONS DURING CHEMOTHERAPY B NYQUIST, *Acta ophth* 21:61, 1944

Two cases of retinitis complicating chemotherapy are reported. A woman aged 52 had slight retinitis in one eye, together with jaundice and an exanthem, in the course of mild erysipelas, which was treated with a sulfonamide drug The fundus was normal when the patient was seen again, four months later

A woman aged 57 while undergoing treatment for pneumonia with sulfathiazole exhibited a dense macular exudate, together with hemorrhages, in both eyes The lesions cleared in six months, but small residual central scotomas remained The author is not sure whether these complications are related to the drugs or to the underlying disease process

O P PERKINS

### **Glaucoma**

THE PRODUCTION OF A FILTERING CICATRIX IN GLAUCOMA RICHARD CRUISE, *Brit J Ophth* 31:265 (Feb) 1947.

Cruise obtained for microscopic examination an eye on which he had performed a successful hinged flap sclerotomy twelve years previously Microscopic observations by E Wolff substantiated the theory on which the operation was based—the establishment of permanent drainage from the anterior chamber by means of incisions alone, without excision of any tissue The technic of the operation is as follows:

A flap of conjunctival and subconjunctival tissue is dissected down to the limbus, the cornea being split for 0.5 mm A special hook with a very sharp point is inserted into the corneosclera just above the limbus, so as to get a firm hold of the eyeball The anterior chamber is entered by dissecting through the sclera 1.5 mm from the limbus with a scalpel or a Graefe knife for a distance of 5 mm If the aqueous is permitted to escape slowly, the iris does not prolapse If it does, it can be replaced with a repositor and there will be no tendency for protrusion of the iris when the posterior chamber is empty While the corneoscleral lip of the incision is held with the hook, with a pair of sharp-pointed scissors two lateral cuts of 2 mm are made, one at each end of the incision, and sloped toward each other, so as to make a blunt-angled hinge, with the apex directed toward the cornea The conjunctiva is replaced but not sutured If the conjunctival flap is thick, as it is in some cases in which there is plenty of subconjunctival tissue, a suture that merely keeps the flap from flopping forward may

be inserted, but never pulled tight, as this would tend to hasten healing. By this means an incision of 9 mm. has been made in endothelium-lined tissue, and it is the author's experience that this procedure is adequate to produce an endothelium-paved cicatrix, with minimal risk of prolapse of the iris. Primary union of the corneoscleral flap is prevented by massaging aqueous through the incision under the conjunctiva, the escaped aqueous causing the corneoscleral flap to ride up and delay approximation of its edges. This massage must be done within twenty-four hours and must be continued for a week or ten days, otherwise there will be a tendency to premature union of the edges of the incision. Primary union is delayed deliberately in order to enable endothelial cells to proliferate and insinuate themselves between the cut margins at the expense of the normal connective tissue cells and form a permeable track through the periphery of the anterior chamber. Microscopic study showed that the boggy area of filtration was covered with thinned conjunctival epithelium, containing two to four layers of nuclei. It was limited above by a characteristic papillary-like thickening of the epithelium. The drainage area was largely filled with a delicate spongework of connective tissue, with here and there some fine fibers, which stained like Descemet's membrane. The actual track in the corneosclera was filled with the same spongework of delicate connective tissue as was the drainage area. Here and there, also, were spots of pigment. The walls of the track were lined in part with definite endothelium, while in other parts the sclera was bare, in these parts the incision had apparently undergone no change since the day it was made, about twelve years ago. In many of the sections a portion of Descemet's membrane was seen, no doubt owing to the tendency of this membrane to curl forward when cut.

The author comments as follows: An endothelial lining of filtering scars is usually denied, but there can be no doubt of its presence here. The fact that the sclera has shown no signs of healing appears to bear out Thomson Henderson's theory that tissues bathed by the aqueous are not stimulated to show the usual signs of repair.

The article is illustrated

W ZENTMAYER

### Hygiene, Sociology, Education and History

ESERINE [PHYSOSTIGMINE] ITS HISTORY IN THE PRACTICE OF OPHTHALMOLOGY F H RODIN, *Am J Ophth* 30: 19 (Jan) 1947

Rodin gives an interesting account of physostigmine (eserine) starting with Daniell's description of the Calabar bean (*Physostigma renenosum*), or esère, as the natives of old Calabar (West Africa) called it, and which they used in their judicial procedures. If, after a predetermined period, the accused vomited this poison, he was considered vindicated and was freed of his charge. Robert Christison was the first to experiment with the Calabar bean, and he used himself as a subject. Thomas R. Fraser, his assistant, continued his study and isolated its active principle, physostigmine. Argyll Robertson also experimented with the drug and emphasized its miotic action, but Ludwig Laqueur was the first ophthalmologist to use it for glaucoma.

W S REESE

### Injuries

THE INTRAOCULAR FOREIGN BODY A SERIES OF SEVENTY-TWO CASES  
IN THE B L A H. B STALLARD, Brit J Ophth 31:12 (Jan.)  
1947

An account is given of 72 cases of penetrating wounds of the eye with retained intraocular foreign body in which the patients came to a field hospital in Normandy and a 2,000 bed general hospital in Belgium (British Liberation Army) from July 1944 until the end of hostilities in Europe, in May 1945 Besides battle casualties, the cases represented accidental injuries in field workshops and injuries inflicted by foolish and negligent handling of military weapons Methods of localization with roentgen rays and types of the giant electromagnet are discussed It is pointed out that in military surgical procedures carried out under field conditions such apparatus has to be simple The localization must be used expeditiously by men with no special knowledge or training The average time for a case was three minutes for suturing a limbal ring in place, about ten minutes for the roentgenographic examination and seven to twelve minutes for the operation of extraction of the foreign body by the scleral route Visual results at the time of evacuation ranged from 6/5 to no perception of light (2 cases) Two eyes were ultimately excised The scleral route for extraction is indicated in the majority of cases and is simpler and less traumatic than the anterior route With careful technic, the danger of loss of vitreous is negligible This complication did not occur in this series Retinal detachment is mentioned in the literature as a complication of the operation by the scleral route This catastrophe is unlikely to occur as a direct result of the operation when diathermy has been used around the incision in the sclera and intraocular membranes It may have happened in cases in which diathermy was not used, but there is no comment on this point in the literature Retinal detachment is more likely to be due to the pathologic changes induced inside the eye at the time of injury In this series, 69.3 per cent of foreign bodies were extracted, 51.3 per cent by the scleral route and 18 per cent by the anterior route The article is lengthy and is a comprehensive survey of the entire subject of intraocular foreign bodies

W ZENTMAYER

### Lacrimal Apparatus

A SURVEY OF THE RESULTS OF LACRIMAL STRICTUROTOMY I LLOYD,  
Brit J Ophth 31:51 (Jan ) 1947

Lloyd has modified the French method of performing stricturotomy on the lacrimal passages The canaliculus can be dilated sufficiently to allow the passage of the stricturotomy knife with a slight or negligible slit Dilation was performed every two weeks for two months and then discontinued unless indicated by a return of symptoms An analysis of 31 cases showed that mucocele was present in 4 cases, chronic low grade mucopurulent infection of the lacrimal passages in 12 cases, and bilateral obstruction in 10 cases The effects of the operation were traced in 29 cases Complete cure resulted in 15 cases (52 per cent)



and "improvement" in 7 cases Symptomatic relief satisfactory to the patient was obtained in 76 per cent of cases There were 7 failures

W ZENTMAYER

### Lens

PROLIFERATION OF THE EPITHELIUM OF THE LENS B SAMUELS,  
Am J Ophth 30:1 (Jan) 1947

Samuels summarizes a study of the proliferation of epithelial cells of the lens in 185 cases of nontraumatic cataract The lenses that showed the greatest proliferation were in the eyes with corneal scars, spontaneous iritis and detachment of the retina These were the eyes in which a low grade, chronic alteration in the metabolism had existed over the longest period

The lenses that showed the least proliferation belonged in the eyes with intraocular tumors and glaucoma Death of the cells characterized the cases of tumor, owing to the irritant poisons eliminated by the tumor as it became necrotic That multiplication of cells was seldom seen in the glaucomatous globes was probably due to the fact that the cells were compressed between the swollen lens substance and the distended capsule This may be the reason that in cases of glaucoma an anterior polar cataract is a clinical rarity

W S REESE

STARS OF THE CRYSTALLINE LENS AND ARRANGEMENT OF ITS FIBERS  
PERSONAL OBSERVATIONS M DRUAULT, Arch d'opht 6:16, 1946

The embryonic development of the stars of the lens is reviewed The author points out that the anterior Y is upright and the posterior one inverted There is considerable variation in their exact positions, and the author presents a review of the studies which have been made in the literature, as well as his own He calls attention to the fact that in the older observations the stars were located between the fetal nucleus and the cortical layers With the slit lamp they have more recently been seen between the embryonic and the fetal nucleus

S B MARLOW

### Neurology

CHANGES IN SENSORY ADAPTATION TIME AND AFTER-SENSATION WITH  
LESIONS OF PARIETAL LOBE M B BENDER, Arch Neurol & Psychiat 55:299 (April) 1946

Bender summarizes his article as follows "A patient with gunshot wound of the left posterior parietal and occipital lobes showed disturbances in visual, cutaneous and proprioceptive senses on the right side of his body These defects were elicited under special conditions Whereas with single stimulation his vision appeared to be intact, simultaneous stimulation of his right and left fields of vision caused the image on his right to become extinct This phenomenon of extinction was found in various forms, from fluctuation and blurring to complete invisibility of an image A similar phenomenon was found for cutaneous perception

"Another patient, with a gunshot wound in the left anterior parietal and posterior frontal lobes, showed motor and sensory disturbances in the right side of his body. The sensory changes could be elicited only under special conditions and were expressed as a prolongation of the periods of sensory adaptation and after-sensation. With paired equal stimulation, sensation was apparently enhanced on the affected side. With paired simultaneous stimulation in which a strong stimulus was applied to the left side and a weak stimulus to the right side, there was reduction of sensory adaptation time, and even extinction of sensation. This case illustrates the phenomenon of 'enhancement or extinction' of sensation, either of which could be obtained on stimulating the same area of skin at different times under different conditions. . . . These patients also showed decrease of increase in after-sensations.

"These observations reveal that most of the disturbances in these patients were due to normal mechanisms (such as rivalry with resultant dominance, sensory adaptation and after-sensations) which became apparent under pathologic conditions, such as lesions in the parietal lobe. Why these mechanisms became apparent is not clear. Without the foregoing considerations and special investigations of sensations, most of the symptoms could not be explained, because routine neurologic examination for sensation revealed an essentially normal status in both these patients."

S R IRVINE

PHENOMENA OF SENSORY SUPPRESSION N REIDER, Arch Neurol & Psychiat 55: 583 (June) 1946

"Clinical studies on suppression phenomenon are reported in which stimuli originating in a normal, or relatively normal, sensory field tended to inhibit or abolish the perception of stimuli arising from an 'affected' field.

"When this phenomenon involves vision, in the presence of normal visual acuity and normal perimetric fields, it may be mistaken for a post-traumatic neurotic reaction. The mechanisms underlying the pathophysiologic changes are discussed, emphasis being placed on the fact that the phenomenon may be elicited not only by contralateral but by homolateral stimuli. Theoretic implications of the phenomenon are mentioned."

These conclusions were derived from careful and detailed study of 2 cases of head injury, with subsequent continued visual complaints in 1 case and suppression of cutaneous sensation in the other.

S R. IRVINE

ABNORMAL DELAY OF VISUAL PERCEPTION E SACHS, Arch Neurol. & Psychiat 56: 198 (Aug) 1946

The diagnostic method Sachs describes makes use of a peculiar visual phenomenon which makes possible recognition of minute unilateral delays in perception of visual impulses. Taking advantage of the high degree of sensitivity of visual reception, the method promotes recognition of the disturbed function of the optic nerve at an earlier stage than is obtainable with existing methods.

When a normal observer looks at a pendulum swinging in front of an illuminated background and a smoked glass is placed in front of one eye, the pendulum appears suddenly to describe a horizontal circle. This stereo-effect, the so-called Pulfrich effect, results from a lag of perception in the eye behind the smoked glass. The physiologic basis is probably slower conduction of impulses and/or transmission of the weaker of the two, otherwise identical, stimuli.

This normal Pulfrich effect is elicited by a brightness difference of certain magnitude between the illuminations of the two eyes. It is assumed that in persons with a pathologic condition of one optic nerve abnormal delay in conduction and/or transmission of impulses may be an early occurrence. This delay, however, at its early stage may be below the threshold of perceptibility, requiring a special "magnifying" device for demonstration.

The assumption is made that for persons with such subthreshold delay the light intensity for the eye on the affected side requires less reduction than for a normal observer in order to make the Pulfrich effect manifest.

A simple method of producing and measuring the Pulfrich effect by means of a moving rod and two pairs of polaroids is described.

Relations of the Pulfrich effect, static stereopsis and perception of movement and the site and cause of the abnormal Pulfrich effect are discussed, and the study of correlations between the abnormal effect and histopathologic changes is suggested.

S R IRVINE

#### RING SCOTOMA AND TUBULAR FIELDS THEIR SIGNIFICANCE IN CASES OF HEAD INJURY M B BENDER and H L TEUBER, Arch Neurol & Psychiat 56: 300 (Sept ) 1946

After injury to the brain, apparent ring scotomas, concentric contraction of visual fields, shifting and "spiral" fields may be found with specific methods of examination of the fields. Different types of fields may be encountered in one and the same case. However, the changes observed vary consistently and directly with the different methods of plotting. The authors illustrate this in a case which was studied with neurologic, psychophysiologic and phenomenologic methods. The unusual field changes, viz, ring scotomas and contracted and spiral fields, as well as severe disturbances in visual perception (haziness, fragmentation and obliteration of images from the periphery inward), seemed to be produced by a continual fluctuation in the visual threshold for different parts of the field, with concomitant phenomena of extinction. It is concluded that such ring scotomas, despite their variability, are not psychogenic, but have an organic basis.

S R IRVINE

#### Operations

##### IMPLANTATION INTO TENON'S CAPSULE S A Fox, Am J Ophth 29: 1571 (Dec ) 1946

Fox describes a technic of implanting a plastic ball in Tenon's capsule after enucleation. He emphasizes the use of a snare to amputate the globe, and a conformer with a monocular dressing to prevent extrusion of the globe.

W S REESE

## CONTRIBUTIONS TO TOTAL BLEPHAROPLASTY I CZUKRÁSZ, Brit J Ophth 31:108 (Feb) 1947

Czukrász describes 3 cases in which three different methods of substituting for a total lack of eyelids were employed. The first procedure employed was that of Hughes, which is adapted to restore the upper and the lower lid. Blaskovic's second operation is suitable when the whole upper lid is missing. The Hungarian plastic procedure generally is used for substituting the lower lid only, but in cases in which both lids are missing the author recommends the sliding flap, moreover, if one hopes to save the bulb, the method offers the advantage of being able to replace at once the upper and the lower lid with one plastic arch.

The article is illustrated

W ZENTMAYER

## TECHNIC OF GRAFTING THE HUMAN CORNEA G-P SOURDILLE, Arch d'opht 6:273, 1946

The author describes his technic of grafting the cornea. One of the most important points is the use of a spatula designed to protect the lens while removing a piece of the cornea by trephining. The author is convinced that, in spite of many accidents, a good result is possible.

S B MARLOW

## Orbit, Eyeball and Accessory Sinuses

## REMOVAL OF THE WRONG EYE H M TRAQUAIR, Brit J Ophth 31:8 (Jan) 1947

The most terrible disaster which can occur to the ophthalmic surgeon and to the patient is "removal of the wrong eye." It might be thought that this accident is merely a possible, but unlikely, danger, about which teachers should warn students but which has never actually occurred. There is, nevertheless, abundant evidence that this catastrophe has actually occurred. The earliest reference to the matter which the author found was that of Mauthner, who wrote in 1881 that he had been present when the mistake was nearly made in a case of sympathetic ophthalmia. A quotation from Elschnig indicates that a case had occurred within his knowledge. The author states that of over 60 textbooks on ophthalmology and ophthalmic surgery published prior to 1898 examination of 37 available revealed mention of the subject in only 1. Only 4 of 14 books published since 1898 and 2 later editions of older work (Lawson and Czermak) contain such references. Recent works do not mention the subject, Sattler (von Graefe, F, and Saemisch, T. Handbuch der gesamten Augenheilkunde, Leipzig, W Engelmann, 1922 [Sattler]) appears to give the latest reference. Of 8 direct references, only 1 is British, the rest being German and American. The diseases concerned, in actual instances, have been intraocular tumor, glaucoma and sympathetic ophthalmia, probably chiefly the first. Nothing is known as to even the approximate number of cases. As might be expected, in every known case a general anesthetic was used. In operations on infants and young children the risk must be taken, and it is the duty of the surgeon to take proper precautions personally, and not to delegate such an important

responsibility The eye should be examined immediately before the operation, while the patient is on the table If a general anesthetic is to be given either to an adult or to a child, administration should not be commenced until the surgeon is present

The only infallible preventive, if any measure can be infallible, is the use of local analgesia This method should be adopted in all cases of adults in which the eye to be removed does not obviously and distinctly differ in external appearance from the other A paragraph on this subject should be included in every textbook in which removal of the eye is mentioned

W ZENTMAYER

### Physiology

FUNCTION OF THE PIGMENTED EPITHELIUM AND THE NEUROEPITHELIAL LAYERS OF THE RETINA L MAGGIORE, *Ann d'ottal e clin ocul* 72:1, 1946

The author considers the behavior of visual function in cases of detachment of the retina He shows that the light sense is in many cases partially reestablished after surgical intervention because of the rapidity with which the subretinal fluid is eliminated, together with some unknown behavior of the layer of rods and cones and the pigmented epithelium On the basis of his previous investigations on the persistence of certain visual functions in cases of partially detached or incompletely reattached retina, he formulates the following hypothesis Since the subretinal fluid layer is rather thin, the electrons liberated by the effects of light on the pigment cells (Schanz's theory) can influence the behavior of the rods and cones It follows that the classic concept of the need for intimate contact between the neuroepithelial and the pigmented epithelial layer is of value only when perfect visual function is intended A partial retinal function is, in fact, possible within certain limitations

G B BIETTI

### Retina and Optic Nerve

POSTNEURITIC OPTIC ATROPHY IN REPATRIATED PRISONERS OF WAR  
W L ROBERTS and T H WILLCOCKSON, *Am J Ophth* 30:165  
(Feb) 1947

Roberts and Willcockson report 6 cases of visual impairment of nutritional origin, in none of which did any improvement result from intensive dietary therapy In all but 1 case there was a history of beriberi or pellagra, and in all the patients had suffered severe malnutrition with serious loss of weight In all but 1 case the fields showed bilateral absolute central or paracentral scotoma, but the peripheral fields were constricted in only 2 cases

W S REESE

NUTRITIONAL RETROBULBAR NEURITIS F D CARROLL, *Am J Ophth* 30:172 (Feb) 1947

Carroll refers to and discusses Whitbourne's work in Jamaica, West Indies, and his own observations on former Japanese prisoners at the Valley Forge Hospital and concludes that the syndromes in the two

groups are similar. He reports the case of a man aged 24 who had lived in Jamaica all his life. Vision was 20/200 in each eye, and the patient had dense centrocecal scotomas.

W S REESE

CONCENTRIC BODIES IN THE SHEATH OF THE OPTIC NERVE. THEIR SIGNIFICANCE AND CLINICAL INTEREST. G OFFRET, *Arch d'opht* 6: 29, 1946

In this article, the author refers to the corpora amylacea. He reviews their histologic character and presents photomicrographs of these bodies. He calls attention to their location in the sheath of the optic nerve and the arachnoid of the brain. From his studies, he concludes that these bodies are derived from the meningoblast. They are observed in the adult in the depths of the dura and are sometimes calcified. They are histologically similar to the bodies present in the meninges of the brain and in meningiomas. A number of photomicrographs illustrating the points which the author makes are presented.

S. B MARLOW

### Tumors

INHERITANCE OF RETINOBLASTOMA. TWO FAMILIES SUPPLYING EVIDENCE. H F FALLS, *J A M A* 133: 171 (Jan 18) 1947

Two new pedigrees are presented which lend support to evidence that retinoblastoma is a hereditary form of neoplasia. The first case was that of a girl aged 6 months. The diagnosis was bilateral retinoblastoma. There was minimal intraocular calcification in both eyes. Enucleation of the right eye was advised for pathologic study. The parents refused consent. In a twin sister, seen at the age of 11 months, a bilateral gray reflex had been observed at the age of 6 months. The diagnosis was bilateral retinoblastoma. Bilateral enucleation or roentgenotherapy was advised but consent was refused. In the first child spontaneous rupture of the globe occurred at the age of 9 months. The second child died at the age of 13 months of reported intracranial and posterior orbital extension. The first child wasted away in cachexia. There was intracranial and posterior orbital extension.

In the second family a girl aged 3½ years had the left eye removed for retinoblastoma. The history revealed that ocular tumors were common in the sibship of the child's mother. The mother had her left eye removed for retinoblastoma at the age of 3½ years. Five of the 9 siblings had a condition diagnosed as retinoblastoma. Two of those affected survived to reach child-bearing age.

The author summarizes his observations as follows. A family was observed in which retinoblastoma occurred bilaterally in identical female twins. In a second family both the horizontal and the vertical occurrence of retinoblastoma was observed. Retinoblastoma may have different genotypes, and it is not necessary to interpret all pedigrees in terms of a single mechanism of inheritance. Parents who have produced a child with retinoblastoma should be urged to discontinue having children, and children surviving enucleation for retinoblastoma should be sterilized.

W. ZENTMAYER

## Uvea

UVEITIS AND NICOLAS-FAVRE-DURAND DISEASE [LYMPHOGRANULOMA VENEREUM] C GARBINO, Arch de oftal de Buenos Aires 21:88 (April-June) 1946

The case histories of 4 patients with uveitis of an unknown cause are given. In all 4 cases the Frei test gave a positive reaction. Treatment with antimony and potassium tartrate gave excellent results. The author believes that in all cases of uveitis of unknown origin a Frei test should be made.

M E ALVARO

PENICILLIN THERAPY. BILATERAL ENDOGENOUS UVEITIS. R LACHMAN and E P CHACÓN, Arch de oftal de Buenos Aires 21:94 (April-June) 1946

A complete cure, with recovery of vision in both eyes within a short time, in a case of severe bilateral endogenous uveitis with hypopyon and low tension was obtained with penicillin. An initial dose of 20,000 units of penicillin was administered, with 15,000 units every three hours thereafter, 120,000 units were administered daily for eight days. At that time the authors again examined the patient. Vision was 10/10 in each eye. Corneal precipitates and slight pigment were present on the anterior capsule of the lens. The iris was normal. No other lesions were noted biomicroscopically.

M E ALVARO

IRIDOCYCLITIS AND INFECTED VARICOSE ULCER. O SILVEIRA, Ophthalmos 3:3, 1944

From the case observed, it is believed that there was a correlation between the iridocyclitis and the infected varicose ulcer, because the ocular disease proved incurable until the veins which formed the ulcer, also incurable, were excised; the iridocyclitis and the varicose ulcer were cured without other treatment.

M E ALVARO

## Vision

THE MIDDLE EAST ADAPTOMETER. W H WILSON, Brit J Ophth 30:645 (Nov) 1946

Wilson describes in minute detail the construction of an adaptometer devised for the army medical service in the Middle East. The primary purpose of the apparatus was to test the limits of dark adaptation in the considerable number of men complaining of night blindness and later to determine whether the night vision of men on special duties, such as night driving, was sufficiently good.

W ZENTMAYER

## Book Reviews

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**Alterations de la rétine en rapport avec les affections générales Atlas ophtalmoscopique II.** By Paul Bonnet Pp 253, with 36 plates in color Paris Masson & Cie, 1947

This report on retinal disorders related to systemic diseases was presented to the *Société française d'ophtalmologie* on May 15 1947, and is the work of Paul Bonnet, professor at the ophthalmic clinic in Lyons This is part 2 of the ophthalmoscopic atlas, of which part 1, on diseases of the retina, by Gabriel Renard, was published in 1946 and previously reviewed in the ARCHIVES (38: 129 [July] 1947)

The general diseases studied in this book are those of the blood The retinal conditions enumerated are cyanosis of the retina, intracranial aneurysm, various types of leukemia, malignant Hodgkin's disease (lymphogranulomatosis), anemias, angiomatosis (Rendu-Osler disease), hemolytic jaundice, Banti's syndrome (splenomegaly of undetermined origin), hemorrhagic diathesis, the effects of thorium X, general infections and certain forms of diabetes The discussion of each condition is prefaced by a short introduction on the fundamental medical illness, followed by a description of the ophthalmoscopic picture and its diagnosis Illustrative case histories give the complete medical findings and the particular ophthalmoscopic picture, with an interesting discussion on its semilogic importance and comments on the information that the often neglected examination of the eye would give to the internist In addition to the 47 drawings in the text, there are 36 plates in color, which illustrate the lésions described in the text and are the important part of the volume The colored illustrations are well drawn and quite up to the high standard of reports of the French society They are the work of the *Société de photo-chromo-gravure of Lyons*

This volume brings many interesting and unusual ophthalmoscopic pictures, particularly that of leukemia It should be of value to the internist as well as to the ophthalmologist, and illustrates the closer relation which is developing between ophthalmology and internal medicine

Dr Bonnet has made a valuable contribution with this study, which has been carried on over a number of years, and the French Society of Ophthalmology deserves the gratitude of all ophthalmologists for its publication

ARNOLD KNAPP

**Clinical Methods of Neuro-Ophthalmologic Examination.** By Alfred Kestenbaum, M D Price, \$6.75 Pp 384, with 64 illustrations New York Grune & Stratton, Inc, 1946

This book presents the methods of neuro-ophthalmologic examination which are essential for diagnosis in neurology and represents the author's twenty-five years of clinical work in neurologic services Though the methods of neuro-ophthalmologic examination have gained by the introduction of more precise methods, owing to the conditions frequently



present, the simplest methods often have to be relied on. The book occupies, as the author says, a kind of intermediate position and aims to be a supplement to the larger books on neurology of the eye. The necessary anatomic data have been schematized, and certain groups of diseases which affect both the central nervous system and the eye have been omitted. General schematic rules are suggested as a help to the physician in arriving at a diagnosis. The findings indicated, in brief, are of value only when taken in combination with other signs and symptoms.

The book begins with a description of the anatomy of the optic pathways and of the field of vision and its defects. The author then takes up diseases of the optic nerve, chiasmic and retrochiasmic lesions, palsies of the ocular muscles, gaze movement and gaze palsy, nystagmus, disturbance of symmetric movement of the eyes, the disturbances of the palpebral fissure and functional disturbances. A short chapter is given over to the description of the routine neuro-ophthalmologic examination. A glossary, a bibliography and an index conclude the volume.

In this book the neurologist will find a description of ophthalmologic methods of diagnosis, and the ophthalmologist will welcome the aid in arriving at a solution of the neurologic problems which he finds so difficult, even though the material is by no means easy reading. The book contains an enormous amount of information, which should be of great value and can be warmly recommended to those for whom it was written.

ARNOLD KNAPP

**Oculus The Eye** Edited by K Steindorff† and F P Fischer, Utrecht, Netherlands, J S Friedenwald, Baltimore, and Arnold Sorsby, London. *Tabulae biologicae*, volume 23. Price, 70 Dutch gulden. Pp 412, with 11 plates and 87 figures. Dr W Junk, Amsterdam, Netherlands, 1947.

Part 1, on anatomic data, contains the following articles: *Das Auge der Wirbellosen*, H Kahmann, Munich, Germany, *Metrische und deskriptive Merkmale des menschliche und tierischen Auges*, S Oppenheim, Utrecht, Netherlands, *Embryologie de l'oeil des vertébrés*, C Dejean and F Granel, Montpellier, France, *La pupille des vertébrés*, J Nordmann, Strasbourg, France, *Deskriptive Anatomie des Auges der Wirbeltiere und des Menschen*, K Steindorff, Milan, Italy, *Der intraokulare Druck*, *Der Augengefässdruck*, K W Ascher, Prague, Czechoslovakia, and Cincinnati.

Parts 2, 3 and 4, which will cover chemical and physiologic data, are in press and will be published as soon as possible.

† Deceased

ARNOLD KNAPP

**Gifford's Textbook of Ophthalmology** Revised by Francis H Adler, M D. Fourth edition. Price, \$6. Pp 512, with 310 illustrations. Philadelphia. W B Saunders Company, 1947.

In this revision of Gifford's textbook, Dr Adler has been guided by the original purpose of the book to make it suitable for the medical student and for the general practitioner. As instruction in the fundamentals is essential, the author has given a more complete discussion

of the subject of the visual field, and there is a new chapter on "Disturbances of Ocular Motility," written from a physiologic approach. Consideration of orthoptics and operations on the ocular muscles has been omitted. The discussion of refraction is condensed. New chapters treating "Ocular Disorders Due to Diseases of the Central Nervous System" and "Ocular Manifestations of General Diseases" will be found interesting and will appeal particularly to the general practitioner. The discussion of operative treatment is limited to a short chapter.

While the book in its present form, with the revisions and additions just enumerated, seems greatly changed, much has been retained of its former character. Some of the additions appear to the reviewer as rather advanced for the average medical student and the general practitioner, but their worth may come in the later years of practice.

This book in its new edition should continue to hold its popularity with the medical public and serve as an excellent introduction to the study of ophthalmology.

ARNOLD KNAPP

**Contact Lenses** By Theo E Obrig. Second Edition. Price, \$8. Pp 560, with 204 illustrations. New York: Obrig Laboratories, Inc., 1947.

This is the second edition of Obrig's classic work, the first edition of which has already been reviewed in these ARCHIVES (28: 564 [Sept] 1942). The statements then made still apply, but certain additions can be found in this edition. For example, new methods of molding are discussed, and the author's present technic is carefully described. He illustrates each device and procedure—casting shells, preparing the patient, making the mold and cast and duplicates of castings—by means of photographs, some of them new, and all of them excellent. Other additions include a new positive system of fitting, new information on solutions and a chapter on plastics. The bibliography has been brought up to 1946.

So far as the reviewer knows, this is the definitive textbook on contact glasses. Indeed, he knows of no other publication on the subject that approaches the compass of this scholarly work.

G M BRUCE

**Diseases of Children's Eyes** By James Hamilton Doggart, M A, M D (Cantab), F R C S. Price, \$10. Pp 288, with 210 illustrations, including 32 color plates. St Louis: C V Mosby Company, 1947.

From time to time attempts have been made to treat in print the problems of ophthalmology in its relation to children. The project has been undertaken in textbook form (Peters, A. *Die Erkrankungen des Auges im Kindesalter*, Bonn, F. Cohen, 1910) and by means of contributions to the so-called medical systems (Doyne, P. G. *Diseases of the Eyes*, in Thursfield, H., and Paterson, D. *Diseases of Children*, London, Edward Arnold & Co., 1934, pp 1086-1093; Terrien, F. *Maladies de l'oeil et de ses annexes*, in *Traité de médecine des enfants* Nobécourt, P., and Babonneix, L. Paris, Masson & Cie, 1934, vol 4, pp 805-837). Nowhere have these efforts been notably successful, for there is no essential difference between adult and infantile ophthalmic

disease True, there are minor anatomic differences, but if one eliminates hereditary defects (which, after all, usually continue into adult life), diseases of the eye that attack children and children only are few and far between Moreover, most ocular lesions, with but few pertinent exceptions, run in children a course identical with that observed in adults Faced with these unavoidable difficulties, an author has but one recourse—he must write a general textbook in which he points out from time to time the peculiarities of each disease when it attacks children This is precisely what Dr Doggart has done, and he has done it so well that this volume, as it stands, would make an excellent textbook on ophthalmology He points out that the ophthalmologist who undertakes the care of a child has to depend on a second-hand history, and cannot carry out subjective tests and elaborate methods of examination Methods of overcoming these basic defects are mentioned from time to time, and the rest of the book is standard textbook material There is included a chapter on "Ocular Welfare" but a similar discussion is to be found in some other textbooks, notably that of Parsons

The illustrations are excellent, but familiar I believe that I have seen nearly all of them elsewhere

In general, this book will appeal chiefly to residents in ophthalmology and young ophthalmologists Some of the chapters will be of interest to general practitioners and pediatricians

G M BRUCE

**Office Treatment of the Eye** By Elias Selinger, M D Price, \$7.75  
Pp 542, with 67 illustrations Chicago The Year Book Publishers, Inc, 1947

This book is probably the most complete volume on ocular therapy that has appeared in recent years It is a large book, yet it is well organized, with an excellent index, so that it should make a convenient reference text While the material presented is largely the viewpoint of the author, the great majority of his ideas are orthodox and represent standard procedures that are generally accepted

One of the important features of this book is the minute detail with which simple procedures, such as the removal of a conjunctival foreign body, are described The careful presentation of fundamentals should make it of particular value to the beginner in ophthalmology There is also such a wealth of material, obviously drawn from vast experience, that even the older practitioner should find much of interest and value

Of course, no one will agree with everything in this book Many will feel that the author has included much material that does not properly belong within the limits of office practice Some may criticize him for attempting to include a discussion of refraction, which must of necessity be incomplete To this reviewer, none of these criticisms is important, as they are completely outweighed by the vast amount of valuable material in the book

There is no doubt that the author of this book has had a rich experience in the practice of ophthalmology, extending over many years That he has had the ability to record this experience in a highly readable form and the patience to put down the most minute details make it an accomplishment of high order

MAYNARD WHEELER

**The 1947 Year Book of Eye, Nose and Throat.** Edited by Louis Bothman, M D, and Samuel J Crowe, M D Price, \$3.75 Pp 487, with 43 illustrations Chicago The Year Book Publishers, Inc, 1947

This Year Book, in a compact and handy manner, contains an accurate review of the previous year's publications in ophthalmology, with an excellent index to subject matter and authors. The abstracts are well chosen, and in presenting the special topic, "Suggestions for Accurate Records in Ophthalmology," the author of the section on the eye, Dr Louis Bothman, brings Elschnig's classification of normal optic disks and the method of recording lesions of the fundus, as described in Dr Alfred Kestenbaum's book entitled "Clinical Methods of Neuro-Ophthalmologic Examination." The comments by the author are set forth clearly and are well worth reading. The part on the eye occupies 222 pages, and under the heading "General and Miscellaneous" are brought a number of important abstracts, of which may be mentioned "Vascular Basis of Allergy of Eye and Its Adnexa," "Ocular Toxoplasmosis," "Pigmented Tumors" and "Congenital Encephalo-Ophthalmic Dysplasia."

The book maintains the high standard previously established and will be found useful for its practical approach by all ophthalmologists

ARNOLD KNAPP

**Relation of Diseases of the Eye to Diseases of the Nose and Sinuses** (Published in Spanish) By Dr Adolfo Gutmann Pp 40 San Antonio, Chile, Librería Nacimiento, 1947

The author, formerly of Berlin, stresses the importance of diseases of the nose and sinuses in the causation of diseases of the extraocular structures. Besides the direct spread of diseases of the nose to the eye, chronic conditions can produce a sensorial or a vasomotor reflex in the eye and give rise to neuralgias and chronic edema of the lids and orbital tissues.

Sinusitis may result in the spread of an acute infection to the orbit and lead to exophthalmos and displacement of the globe by the formation of a mucocele. Infections of the posterior ethmoid cells and of the sphenoid sinus can cause peripheral contraction of the visual fields and central scotoma. In cases of central scotoma in which the blood, spinal fluid and nervous system are normal and no clearcut infection of the sinuses is found, opening the posterior ethmoid cells and the sphenoid sinus may improve the scotoma.

In cases of exophthalmos help in differential diagnosis is obtained by use of the priesimeter. This instrument is much like a tonometer and is graduated on a scale of 0.1 mm. It is applied to the cornea and a weight of 25 Gm added. In a case of edema of the orbit the globe is pushed back, this does not happen when a solid mass is the cause of the exophthalmos. Both eyes must be measured and the results compared. In the normal eye the reading average is 11 mm. In a case of exophthalmos due to edema of the orbital tissues the globe can be pushed farther back into the orbit than in the case of a solid orbital tumor. In the latter it may not be possible to push back the globe at all.

HUMBERTO ESCAPINI

**Ophthalmology: Section XII of Excerpta Medica.** Amsterdam, Netherlands N V Excerpta Medica, 1947

*Excerpta Medica* is a monthly journal, published in English, of the world's medical literature, comprising fifteen sections and covering the whole field of theoretic and clinical medicine

The *Excerpta* is under the general editorship of M W Woerdeman, chairman, professor of anatomy in the University of Amsterdam, A P de Kleyn, professor of otolaryngology, and W P Zeeman, professor of ophthalmology, also of the University of Amsterdam The board of editors for section XII, which is devoted to ophthalmology, is composed of ophthalmologists from all over the world, including nine from the United States The subeditor is Dr J E Winkelman, of Amsterdam The first three issues of volume I, section XII, are now published and are an outstanding contribution to ophthalmic literature The editors have set themselves a number of objectives, which seem to have been well lived up to in the first three issues Completeness is the first objective, and the aim is to abstract every available article on ophthalmology appearing in the medical literature of the world The length of the abstract varies from merely a mention by title to one sufficiently elaborated to allow the reader to judge for himself the importance of the original article and the basis for the author's statements

Each issue is divided into eleven sections, as follows (1) textbooks, manuals and monographs, (2) the history of ophthalmology—ophthalmology in its relation to the visual arts, (3) anatomy, embryology and ontogenetic development of the visual apparatus, (4) general and experimental physiology and pathology of the eye, (5) methods of examination, (6) hygiene and social medicine as they apply to ophthalmology, (7) special clinical ophthalmology, (8) therapeutics and pharmacology, (9) surgery, (10) comparative ophthalmology, (11) miscellaneous

The type and paper are excellent, and, what is even more important, the English used is good This is a welcome addition to the abstracting services already available in our journals, and Dr Zeeman and his co-editors are to be congratulated on having done ophthalmology a splendid service

Subscriptions can be obtained by writing to the agent for *Excerpta Medica* in the United States, namely, the Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2 For Section XII the subscription rate is \$15 per year

FRANCIS HEED ADLER

# Directory of Ophthalmologic Societies \*

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\* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date

## FACULTY OF OPHTHALMOLOGISTS

President Sir Stewart Duke-Elder, 63 Harley St, London, W 1, England  
 Secretary Mr Frank W Law, 45 Lincoln's Inn Fields, London, W C 2, England

## GERMAN OPHTHALMOLOGICAL SOCIETY

President Prof W Lohlein, Berlin  
 Secretary Prof E Engelking, Heidelberg

## HUNGARIAN OPHTHALMOLOGICAL SOCIETY

President Prof G Horay, Budapest  
 Assistant Secretary Dr Stephen de Grosz, University Eye Hospital, No 1, Illes-  
 ucca 15, Budapest  
 All correspondence should be addressed to the Assistant Secretary

## MIDLAND OPHTHALMOLOGICAL SOCIETY

President Mr Charles Rudd, 91 Cornwall St, Birmingham 3, England  
 Secretary Mr P Sameson Evans, 51 Calthorpe Rd, Birmingham 3, England  
 Place Birmingham and Midland Eye Hospital

## NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President Mr O M Duthie, 22 St John St, Manchester  
 Secretary Mr William M Muirhead, 70 Upper Hanover St, Sheffield 3  
 Place Manchester, Leeds, Newcastle-upon-Tyne, Liverpool, Sheffield and Bradford,  
 in rotation Time October to May

## OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President Dr Claude Morfet, St George's Terrace, Perth, Western Australia  
 Secretary Dr Arnold L Lance, 135 Macquarie St, Sydney  
 Place Perth, Western Australia Time Aug 15-21, 1948

## OPHTHALMOLOGICAL SOCIETY OF EGYPT

President Prof Dr Mahmoud Lutfi, Ophthalmic Hospital, Giza  
 Secretary Dr Mohammed Abbas El Bakly, Ministry of Public Health, Cairo  
 All correspondence should be addressed to the secretary, Dr Mohammed Khalil

## OPHTHALMOLOGICAL SOCIETY OF HOSPITAL DE NUESTRA SEÑORA DE LA LUZ

Chairman Dr Manuel J Icaza y Dublan, Artes 72, Mexico, D F, Mexico  
 Secretary Dr Jorge Meyran, Ezequiel Montes 135, Mexico, D F, Mexico  
 Place Hospital de Nuestras Señora de la Luz Time Second Friday of each  
 month

## OPHTHALMOLOGICAL SOCIETY OF NEW ZEALAND

President Mr W A Fairclough, Imperial Bldgs, Queen St, Auckland  
 Secretary Dr W J Hope-Robertson, Kelvin Chambers, 16 The Terrace,  
 Wellington

## OPHTHALMOLOGICAL SOCIETY OF SOUTH AFRICA

President Dr A Verwey, Phoenix Chambers, Church St, Pietermaritzburg  
 Secretary Dr J K de Kock, Groote Kerk Bldg, 32 Parliament St, Cape Town

## OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President Dr A J Ballantyne, 11 Sandyford Pl, W, Glasgow C 3, Scotland  
 Secretary Mr J H Doggart, 49 Wimpole St, London, W 1

## OPHTHALMOLOGY SOCIETY OF BOMBAY

President Dr D D Sathaye, 127 Girgaum Rd, Bombay 4, India  
 Secretary Dr H D Dastur, Dadar, Bombay 14, India  
 Place H B A Free Ophthalmic Hospital, Parel, Bombay 12 Time First  
 Friday of every month

OXFORD OPHTHALMOLOGICAL CONGRESS

Master Mr F A Williamson-Noble, 27 Harley St, London W 1, England  
 Secretary-Treasurer Dr F. A. Anderson, 12 St John's Hill, Shrewsbury, England  
 Place Oxford Time July 3-5, 1947

PALESTINE OPHTHALMOLOGICAL SOCIETY

President Dr Arie Feigenbaum, Abyssinian St 15, Jerusalem  
 Secretary Dr E Sinai, Tel Aviv

PHILIPPINE OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr Antonio S Fernando, Philippine General Hospital, Manila  
 Secretary-Treasurer Dr Carlos V Yambao, Philippine General Hospital, Manila

POLISH OPHTHALMOLOGICAL SOCIETY

President Dr W Kapuściński, Libelta 14, Poznań  
 Secretary Dr S Topolski, Piusa 38, Warsaw  
 Place Ophthalmic Clinic, Oczki 6, Warsaw Time Every two years—Summer

PUERTO RICO MEDICAL ASSOCIATION, SECTION OF OPHTHALMOLOGY  
 AND OTOLARYNGOLOGY

President Dr José T Picó, P O Box 3866, Santurce  
 Secretary Dr Ricardo F Fernandez, Instituto Oftálmico, San Juan  
 Place Asociación Médica de Puerto Rico, Santuce

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President Dr Harold Levy, 149 Harley St, London, W 1, England  
 Secretaries Dr P M Moffatt, 115A Harley St, London, W. 1, England Dr  
 A S Philips, 104 Hartley St, London W 1, England

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President Dr Armando Gallo, Rua Benjamin Constant, 67, 9º Andar São Paulo,  
 Brazil  
 Secretary Dr F Amédée Féret Filho, Rua Marconi, 48, 4º Andar, São Paulo  
 Brazil

SCOTTISH OPHTHALMOLOGICAL CLUB

President Dr H M Traquair, 16 Manor Pl, Edinburgh 3  
 Secretary Dr Alexander Garrow, 15 Woodside Pl, Glasgow, C 3  
 Place Edinburgh and Glasgow, in rotation

SOCIEDAD ARGENTINA DE OFTALMOLOGIA

Chairman Dr Jorge Malbrán, Buenos Aires  
 Secretary Dr Benito Just Tiscornia, Santa Fe 1171, Buenos Aires

SOCIEDADE BRASILEIRA DE OFTALMOLOGIA

President Dr Edilberto Campos, Rua Rodrigo Silva 7-1º, Rio de Janeiro, Brazil  
 Secretary Dr Evaldo Campos, R Rodrigo Silva 7-1º andar, Rio de Janeiro, Brazil  
 Place Rio de Janeiro, Brazil Time Third Friday of every month from April  
 to December

SOCIEDAD COLOMBIANA DE OFTALMOLOGIA Y DE OTORRINOLARINGOLOGIA

President Dr Jorge Suárez-Hoyos, Carrera 5a, no 13-39, Bogota, Colombia  
 Secretary Dr Francisco Arango, Calle 20, no 4-51, Bogotá, Colombia  
 Place Club Médico Time Second Tuesday of every month  
 All correspondence should be addressed to the President

SOCIEDAD CHILENA DE OFTALMOLOGÍA

President Prof Dr Halo Martini, Av Salvador, no 300, Santiago, Chile  
 Secretary Dr Adrian Araya, Av Salvador, no 300, Santiago, Chile



## SOCIEDAD CUBANA DE OFTALMOLOGIA

President Prof Lorenzo Comas, Calle D #461, Vedado, Habana, Cuba  
 Secretary Dr Oscar F Horstmann, Calle 5ta #702, Vedado, Habana, Cuba  
 Time Second Tuesday of every month

## SOCIEDAD MEXICANA DE OFTALMOLOGIA

President Dr Feliciano Palomino Dena, Londres 44, Mexico, D F.  
 Secretary Dr Teodulo Agundis Jr, Lucerna 63, Mexico, D F  
 Place Escuela Nacional de Medicina, Venezuela 4, Mexico, D F Time 8 30  
 p m, first Tuesday of each month

## SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President Prof Dr Enrique V Bertolto, Rosario  
 Secretary Dr Juan Manuel Vila Ortiz, Rosario  
 Place Rosario Time Last Saturday of every month, April to November All  
 correspondence should be addressed to the President

## SOCIEDADE DE OFTALMOLOGIA DE GUADALAJARA

President Dr Elias Mendoza González, Guadalajara, Mexico  
 Secretary Dr L Nuñez Leal, Guadalajara, Mexico

## SOCIEDADE DE OFTALMOLOGIA DEL NORTE

President Dr Alberto Cárdenas  
 Secretary Dr Jorge Luis Castillo, Mendoza 421, Tucumán, Argentina

## SOCIEDADE DE OFTALMOLOGIA DE MINAS GERAES

President Prof Hilton Rocha, Rua Rio de Janeiro 2251, Bello Horizonte, Minas  
 Geraes, Brazil  
 Secretary Dr Ennio Coscarelli, Rua Aimorés 1697, Bello Horizonte, Minas Geraes,  
 Brazil

SOCIEDADE DE OFTALMOLOGIA E OTORINOLARINGOLOGIA DO  
RIO GRANDE DO SUL

President Dr Luiz Assumpção Osorio, Edifício Vera Cruz, Apartamento 134,  
 Porto Alegre, Rio Grande do Sul  
 Secretary Dr Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande  
 do Sul

## SOCIEDADE DE OFTALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DO BAHIA

President Dr Theonilo Amorim, Barra Avenida, Bahia, Brazil  
 Secretary Dr Adroaldo de Alencar, Brazil  
 All correspondence should be addressed to the President

## SOCIETÀ OFTALMOLOGICA ITALIANA

President Prof Dott. Giuseppe Ovio, Ophthalmological Clinic, University of  
 Rome, Rome  
 Secretary Prof Dott Epimaco Leonardi, Via del Gianicolo, 1, Rome

## SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary Dr Rene Onfray, 6 Avenue de la Motte Picquet, Paris, 7°

## SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President Prof S Larsson, Lund, Sweden  
 Secretary Dr K O Granstrom, Södermalmstorg 4, Stockholm Sö

SOUTHERN OPHTHALMOLOGICAL SOCIETY, ENGLAND

President Mr J E H Cogan, Tunbridge Wells, England.  
 Secretary Mr Nigel Cridland, 25 Craneswater Pk, Southsea, England.  
 Time From March to October

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President Dr D Arish-Friedman, 96 Allenby St, Tel Aviv, Palestine  
 Secretary Dr Sadger Max, 9 Bialik St, Tel Aviv, Palestine

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION  
 ON OPHTHALMOLOGY

Chairman Dr Everett L Goar, 1300 Walker Ave, Houston, Texas  
 Secretary Dr Trygve Gundersen, 101 Bay State Rd, Boston  
 Place Chicago Time June 21-25, 1948

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY,  
 SECTION ON OPHTHALMOLOGY

President Dr C H McCaskey, 20 N Meridian St, Indianapolis, Ind  
 Executive Secretary-Treasurer Dr William L Benedict, 100-1st Ave Bldg,  
 Rochester, Minn

AMERICAN OPHTHALMOLOGICAL SOCIETY

President Dr Henry C Haden, 1914 Travis St, Houston, Texas  
 Secretary-Treasurer Dr Walter S Atkinson, 129 Clinton St, Watertown, N Y

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC

Chairman Dr Derrick Vail, 55 E Washington St, Chicago 2  
 Secretary-Treasurer Dr Brittain F Payne, 17 E 72d St, New York 2  
 Assistant Secretary-Treasurer Dr Hunter Romain, 111 E 65th St, New York

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President Dr Alexander E MacDonald, 170 St George St, Toronto 5

CANADIAN OPHTHALMOLOGICAL SOCIETY

President Dr R J P McCulloch, 830 Medical Arts Bldg, Toronto 5  
 Secretary-Treasurer Dr J F A Johnston, 174 St George St, Toronto 5

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President Mr Mason H Bigelow, 1790 Broadway, New York 19  
 Secretary Miss Regina E Schneider, 1790 Broadway, New York 19  
 Executive Director Mrs Eleanor Brown Merrill, 1790 Broadway, New York

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON  
 EYE, EAR, NOSE AND THROAT

President Dr Anthony Ambrose, 31 Lincoln Park, Newark  
 Secretary Dr W Franklin Kein, 15 Washington St, Newark 2  
 Place 91 Lincoln Park South, Newark Time 8 45 p m, second Monday of  
 each month, October to May

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Clarence E McClelland, Decatur, Ill  
 Secretary-Treasurer Dr Philip R McGiath, Peoria, Ill

## CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr W S Jones, 521 Sheridan Rd, Menominee, Mich

Secretary Dr G L McCormick, 650 S Central Ave, Marshfield

## HAWAII EYE, EAR, NOSE AND THROAT SOCIETY

President Dr L Q Pang, 52 S Vineyard, Honolulu

Secretary-Treasurer Dr Harold F Moffat, 1415 Kalakaua, Honolulu

Place Pacific Club, Honolulu Time Third Thursday of each month

## INTER-MOUNTAIN OTO-OPHTHALMOLOGICAL SOCIETY

President Dr James A Cleary, 804 Boston Bldg, Salt Lake City

Secretary-Treasurer Dr Homer E Smith, 1105 Medical Arts Bldg, Salt Lake City

Place University Club, Salt Lake City Time 7 00 p m, third Monday of each month, September through May

## NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President Dr Edwin B Dunphy, 243 Charles St, Boston

Secretary-Treasurer Dr Merrill J King, 264 Beacon St, Boston 16

Place Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston Time 8 p m, third Tuesday of each month from November to April, inclusive

## PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President Dr D H O'Rourke, 1612 Tremont Pl, Denver

Secretary-Treasurer Dr C Allen Dickey, 450 Sutter St, San Francisco

## PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Robert Wightman, 1114 Boylston, Seattle, Wash

Secretary-Treasurer Dr Barton E Peden, 301 Stimson Bldg, Seattle 1, Wash

Place Seattle or Tacoma, Wash Time Second Tuesday of each month except June, July and August

## ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Robert C Finger, RFD New Tower, Rockford, Ill

Secretary-Treasurer Dr Vernon C Voltz, 625 Gas-Electric Bldg, Rockford, Ill

Place Rockford, Ill, or Janesville or Beloit, Wis Time Third Tuesday of each month from October to April, inclusive

## SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Harold H Heuser, 207 Davidson Bldg, Bay City, Mich

Secretary-Treasurer Dr V E Cortopassi, 324 S Washington Ave, Saginaw, Mich

Place Saginaw or Bay City, Mich Time Second Tuesday of each month, except July, August and September

## SIOUX VALLEY EYE AND EAR ACADEMY

President Dr J C Decker, 515 Francis Bldg, Sioux City, Iowa

Secretary-Treasurer Dr J E Dvorak, 408 Davidson Bldg, Sioux City, Iowa

SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY  
AND OTOLARYNGOLOGY

Chairman Dr Calhoun McDougall, Atlanta, Ga

Secretary Dr Alston Callahan, 908 S 20th St, Birmingham 5, Ala

Time First week in November

## SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President Dr H L Brehmer, 221 W Central Ave, Albuquerque, N Mex

Secretary Dr A E Cruthrds, 1011 Professional Bldg, Phoenix, Ariz

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President Dr W. M Dodge, 716 First National Bank Bldg, Battle Creek  
 Secretary-Treasurer D. Kenneth Lowe, 25 W Michigan Ave, Battle Creek.  
 Time Last Thursday of September, October, November, March, April and May

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr J Paul McCloskey, 338 Locust St, Johnstown  
 Secretary-Treasurer Dr Fred E Murdock, 28½ W Scribner St, Dubois

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President Dr E C Moulton, 619 Garrison Ave, Fort Smith  
 Secretary Dr K W Cosgrove, 7 Urquhart Bldg, Little Rock

COLORADO OPHTHALMOLOGICAL SOCIETY

President Dr George H Stine, Burns Bldg, Colorado Springs  
 Secretary Dr J Leonard Swigert, 320 Republic Bldg, Denver  
 Place Colorado General Hospital Time 7 30 p m, third Saturday of each month, October to May, inclusive

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR,  
 NOSE AND THROAT

President Dr W H Turnley, 1 Atlantic St, Stamford, Conn  
 Secretary-Treasurer Dr Morton B Arnold, 781 Main St, Williamantic, Conn

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President Dr William O Martin Jr, Doctors Bldg, Atlanta  
 Secretary-Treasurer Dr C K McLaughlin, 666 Cherry St, Macon

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr W E Stewart, 721 Wabash Ave, Terre Haute  
 Secretary Dr Russell A Sage, 23 E Ohio St, Indianapolis

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr C S O'Brien, University Hospital, Iowa City  
 Secretary-Treasurer Dr Carl A Noe, 120-3d Ave S E, Cedar Rapids

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY  
 AND OTOLARYNGOLOGY

President Dr W B Granger, Emporia  
 Secretary Dr George F Gsell, 911 Beacon Bldg, Wichita 2

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr George S Adkins, 121 N President St, Jackson, Miss  
 Secretary-Treasurer Dr Edley H Jones, 1301 Washington St, Vicksburg, Miss

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON  
 EYE, EAR, NOSE AND THROAT DISEASES

Chairman Dr William T Hunt Jr, 1205 Spruce St, Philadelphia 7  
 Secretary Dr Gabriel Tucker, 250 S 18th St, Philadelphia 3

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY  
 AND OTOLARYNGOLOGY

Chairman Dr Ralph H Gilbert, 110 Fulton St E, Grand Rapids  
 Secretary Dr Walter Z Rundles, 620 Maxine Ave, Grand Rapids

## MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr L R Boies, 1427 Medical Arts Bldg, Minneapolis  
 Secretary Dr W L Hoffman, 543 Medical Arts Bldg, Minneapolis  
 Place Minneapolis Club Time 6 00 p m, second Friday of each month from  
 October to May

## MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President Dr H Casebeer, 44 W Park Ave, Butte  
 Secretary Dr Fritz D Hurd, 309 Medical Arts Bldg, Great Falls

## NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha  
 Secretary-Treasurer Dr John Peterson, 1307 N St, Lincoln

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY,  
OTOLOGY AND RHINOLARYNGOLOGY

Chairman Dr C W Buvinger, 50 Washington St, East Orange  
 Secretary Dr Z Laurence Griesemer, 1145 E Jersey St, Elizabeth

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND  
THROAT SECTION

Chairman Dr Maxwell D Ryan, 660 Madison Ave, New York 21  
 Secretary Dr Thomas H Johnson, 30 W 59th St, New York

## NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr V K Hart, 106 W 7th St, Charlotte  
 Secretary Dr J A Harrill, Bowman Gray School of Medicine, Winston-Salem

## NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr E D Perrin, 221-5th St, Bismarck  
 Secretary-Treasurer Dr M T Lampert, Minot

## OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Wilfred Belnap, 833 S W 11th Ave, Portland  
 Secretary-Treasurer Dr C W Kuhn, 1020 S W Taylor St, Portland 5  
 Place Good Samaritan Hospital, Portland Time Third Tuesday of each month

## PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Gilbert L Dailey, Harrisburg  
 Secretary Dr Benjamin F Souders, 143 N 6th St, Reading  
 Place Hotel Penn-Harris, Harrisburg, Pa Time April 23-25, 1948

## RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President Dr N Darrell Harvey, 112 Waterman St, Providence  
 Secretary-Treasurer Dr Linley C Happ, 124 Waterman St, Providence  
 Place Rhode Island Medical Society, Library, Providence Time 8 30 p m,  
 second Thursday in October, December, February and April

## SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Richard W Hanckel, 96A Bull St, Charleston  
 Secretary-Treasurer Dr Roderick Macdonald, 330 E Main St, Rock Hill

## TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr George Burchfield, Maryville  
 Secretary-Treasurer Dr Sam H Sanders, 1089 Madison Ave, Memphis

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President Dr W E Vandevere, 1001 First National Bank Bldg, El Paso  
Secretary Dr E D Dumas, 425 Medical Arts Bldg, San Antonio

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President Dr Thomas E. Hughes, 1000 W Grace St, Richmond  
Secretary-Treasurer Dr Francis H McGovern, 105 S Union St, Danville

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND  
THROAT SECTION

President Dr George Traugh, 309 Cleveland Ave, Fairmont  
Secretary Dr Welch England, 621½ Market St, Parkersburg

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr R F Thaw, 301 Ohio Bldg, Akron, Ohio  
Secretary-Treasurer Dr J C Damitz, 2d National Bank Bldg, Akron 8, Ohio  
Time 6 30 p m, first Monday in January, March, May and November

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr William B Armstrong, 478 Peachtree St N E, Atlanta, Ga  
Secretary Dr Lester A Brown, 815 Doctors Bldg, Atlanta, Ga  
Place Academy of Medicine Time 7 00 p m, fourth Monday of each month  
from October to May

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman Dr Cecil H Bagley, 2 E Reed St, Baltimore  
Secretary Dr F Edwin Knowles Jr, 513 N Charles St, Baltimore  
Place Medical and Chirurgical Faculty, 1211 Cathedral St Time 8 30 p m,  
fourth Thursday of each month from October to March

BIRMINGHAM EYE, EAR, NOSE AND THROAT CLUB

President Each member, in alphabetical order  
Secretary Dr W Chunn Parsons, 425 Woodward Bldg, Birmingham, Ala  
Place Thomas Jefferson Hotel Time 6 30 p m, second Tuesday of each month,  
September to May, inclusive

BROOKLYN OPHTHALMOLOGICAL SOCIETY

President Dr Benjamin C Rosenthal, 140 New York Ave, Brooklyn 16  
Secretary-Treasurer Dr Louis Freimark, 256 Rochester Ave, Brooklyn 13  
Place Towers Hotel, 25 Clark St Time 8 15 p m, third Thursday in February,  
April, October and December

BUFFALO OPHTHALMOLOGIC CLUB

President Dr William H Howard, 389 Linwood Ave, Buffalo 9  
Secretary-Treasurer Dr Sheldon B Freeman, 196 Linwood Ave, Buffalo 9  
Time Second Thursday of each month from October to May

CENTRAL NEW YORK EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Uri Doolittle, University Bldg, Syracuse  
Secretary-Treasurer Dr Alfred W Doust, 306 State Tower Bldg, Syracuse.  
Place University Club Time 7 00 p m, second Wednesday

## CHATTANOOGA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Each member, in alphabetical order

Secretary Dr Douglas Chamberlain, Providence Bldg, Chattanooga, Tenn

Place Mountain City Club Time Second Thursday of each month from September to May

## CHICAGO OPHTHALMOLOGICAL SOCIETY

President Dr Beulah Cushman, 25 E Washington St, Chicago 2

Secretary Dr J R Fitzgerald, 30 N Michigan Ave, Chicago 2

Place Continental Hotel, 505 N Michigan Ave Time Third Monday of each month from October to May

## CINCINNATI GENERAL HOSPITAL OPHTHALMOLOGY STAFF

Chairman Rotate alphabetically

Secretary Dr A A Levin, 441 Vine St, Cincinnati

Place Cincinnati General Hospital Time 7 45 p m, third Friday of each month except June, July and August

## CLEVELAND OPHTHALMOLOGICAL CLUB

Chairman Dr John E L Keyes, 22199 McCauley Rd, Shaker Heights 22, Ohio

Secretary Dr Roscoe J Kennedy, 2020 E 93d St, Cleveland 6

Time Second Tuesday in October, December, February and April

## COLLEGE OF PHYSICIANS, PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Chairman Dr Perce de Long, 37 S 20th St, Philadelphia

Clerk Dr M Luther Kauffman, Medical Arts Bldg, Jenkintown, Pa

Place College of Physicians Bldg Time 8 15 p m, third Thursday of every month from October to April, inclusive

## COLUMBUS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

Chairman Dr M Goldberg, 328 E State St, Columbus, Ohio

Secretary-Treasurer Dr W J Miller, 21 E State St, Columbus, Ohio

Place University Club Time 6 15 p m, first Monday of each month, from October to May, inclusive

## CORPUS CHRISTI EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr Edgar Mathis, 815 Medical Professional Bldg, Corpus Christi, Texas

Secretary Dr June Yates, 210 Medical Professional Bldg, Corpus Christi, Texas

Place Nueces Hotel Time 6 30 p m, third Tuesday of each month from October to May

## DALLAS ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr L Darrough, 4105 Live Oak St, Dallas, Texas

Secretary Dr C A Hofer, 1719 Pacific Ave, Dallas 1, Texas

Place Dallas Athletic Club Time 6 30 p m, first Tuesday of each month from October to June The November, January and March meetings are devoted to clinical work

## DES MOINES ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr H I McPherrin, 406-6th Ave, Des Moines, Iowa

Secretary-Treasurer Dr C C Jones, 1110 Equitable Bldg, Des Moines, Iowa

Time 6 30 p m, fourth Monday of every month from September to May

DETROIT OPHTHALMOLOGICAL CLUB

Chairman Members rotate alphabetically  
 Secretary Dr. Wesley G Reid, 974 Fisher Bldg, Detroit 2  
 Place Club rooms of Wayne County Medical Society Time Second Monday of  
 each month, November to April, inclusive

DETROIT OPHTHALMOLOGICAL SOCIETY

President Dr Bruce Fralick, 201 S Main St, Ann Arbor, Mich  
 Secretary Dr William S Gonne, 619 David Whitney Bldg, Detroit 26  
 Place Hayler's L'Aiglon Bldg Time 6 30 p m, third Thursday of each month  
 from November to April, inclusive

EASTERN NEW YORK EYE, EAR, NOSE AND THROAT ASSOCIATION

President Dr Frank C Furlong, 713 Union St, Schenectady  
 Secretary-Treasurer Dr E Martin Freund, 762 Madison Ave, Albany  
 Time Third Wednesday in October, November, March, April, May and June

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY

President Dr C R Lees, 602 W 10th St, Fort Worth 2, Texas  
 Secretary-Treasurer Dr Van D Rathgeber, 1305 Medical Arts Bldg, Fort  
 Worth, Texas  
 Place Tarrant County Medical Hall, Medical Arts Bldg Time 7 30 p m,  
 first Friday of each month except July and August

HOUSTON ACADEMY OF MEDICINE, OPHTHALMOLOGICAL AND  
 OTO-LARYNGOLOGICAL SECTION

President Dr J Matt Robison, 1304 Walker Ave, Houston, Texas  
 Secretary Dr John H Barrett, 1304 Walker Ave, Houston, Texas  
 Place River Oaks Country Club Time 6 30 p m, second Thursday of each  
 month from October to June

INDIANAPOLIS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr D Hamilton Row, 23 E Ohio St, Indianapolis  
 Secretary Dr J Lawrence Sims, 23 E Ohio St, Indianapolis  
 Place Indianapolis Athletic Club Time 6 30 p m, second Thursday of each  
 month from November to May

KANSAS CITY SOCIETY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Walter L Small, 1103 Grand Ave, Kansas City, Mo  
 Secretary Dr John Clair Howard Jr, 1103 Grand Ave, Kansas City, Mo  
 Time Third Thursday of each month from October to June The November,  
 January and March meetings are devoted to clinical work

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr Robert G Thornburgh, 117 E 8th St, Long Beach 2, Calif  
 Secretary-Treasurer Dr Kirt Parks, 605 Professional Bldg, Long Beach 2, Calif  
 Place Seaside Hospital Time Third Wednesday of each month from October to  
 May

LOS ANGELES OPHTHALMOLOGICAL SOCIETY

Chairman Dr Orwyn Ellis, 727 W 7th St, Los Angeles 14  
 Secretary Dr John A Bullis, 3875 Wilshire Blvd, Los Angeles 5  
 Place 3550 Wilshire Blvd, Los Angeles Time 6 30 p m, third Tuesday of  
 each month, September through June



## LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr William D Donohue, Los Angeles  
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 tember to May

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 month, except June, July, August and September

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 Place Doctors Lounge, Paulsen Medical and Dental Bldg Time 8 p m, last  
 Tuesday of each month except June, July and August

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 Place Medical Society of District of Columbia Bldg, 1718 M St N W, Wash-  
 ington, D C Time 7 30 p m, first Monday of each month from November  
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## DEGENERATION AND REGENERATION OF NERVES IN CORNEAL TRANSPLANTATION

An Experimental Study

HUMBERTO ESCAPINI, M D

NEW YORK

**L**ITTLE work has been done on the degenerative and regenerative nerve changes that occur in the corneal transplant. It has even been thought that reinnervation of the graft has to do with its transparency or opacification.

In 1915 and 1917, Leoz<sup>1</sup> undertook experimental work to study the regeneration of nerves in the corneal transplant. At that time, the technic of corneal transplantation had not yet reached its present development and high percentage of success. Leoz worked mostly with partial and complete circular keratotomies, and the few homotransplants made were rather large, 9 mm in diameter, and circular, and the graft was fastened to the host cornea with interrupted sutures. Only 1 of his rabbits with homotransplants had a partially clear graft, this rabbit was killed eight months after the operation, and a study of its nerves was made. He stated that sixty days after the operation he obtained an anergic oculopalpebral reflex on stimulation of the graft and that histologic preparations of graft showed good regeneration of its nerves in the eighth month.

In 1932 Castroviejo,<sup>2</sup> discussing the recovery of sensitivity in the corneal transplant, stated that in transparent grafts in rabbits he obtained an anergic oculopalpebral reflex three months after the operation.

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The investigation was sponsored by the Resident's Fund, Institute of Ophthalmology of the Presbyterian Hospital.

Submitted in October 1946 in partial fulfillment of the requirements for the degree of Doctor of Medical Sciences of Columbia University College of Physicians and Surgeons. The first part of this thesis, dealing with the normal structure of peripheral nerves and their degenerative and regenerative phenomena, has been omitted for the sake of brevity. Dr Ramón Castroviejo gave invaluable assistance in planning and carrying out this work.

1 Leoz, O. Algunos estudios y ensayos sobre queratoplastias, *Arch de oftal hispano-am* **15** 225-233, 1915, Contribucion de mis estudios experimentales sobre queratoplastia, *ibid* **17** 615-629, 1917.

2 Castroviejo, R. Keratoplasty, *Am J Ophth* **15** 905-916, 1932.

## PRESENT INVESTIGATION

The present study was carried out on albino rabbits weighing 6 pounds (27 Kg). Rabbits are convenient for use in the laboratory, and one may obtain all the material necessary, not only for demonstration of the clearness or opaqueness of the graft but for timing the age of the transplants according to the demands of the work.

With the present development of corneal transplantation, the operation in the human being is successful in a high percentage of selected cases.<sup>2</sup> This percentage of successes is somewhat lower in experimental work on rabbits, owing to the absence of aseptic conditions and the impossibility of keeping the animals from rubbing the grafted eye with the foot or against the cage.

The rabbits used in this work were anesthetized with "pernoston sodium" (sodium 5-sec butyl-5- $\beta$ -bromallylbarbiturate). Two cubic centimeters of a 10 per cent solution of the drug was injected into the peritoneum, and good narcosis was obtained in twenty to thirty minutes. The technic of Castroviejo<sup>3</sup> for the square partial penetrating keratoplasty was followed in all cases.

The rabbits so operated on were kept alive for periods of two weeks to nine months. During this time they were subjected to repeated tests to determine the recovery of corneal sensitivity. Attention was given to the least attempt to blink after stimulation of the cornea.

It is known that man is most suited to the study of the processes of sensory recovery after nerve lesions because he can give verbal information as to the quality of sensation which is felt.

Gutmann and Guttman,<sup>4</sup> studying in rabbits the factors which affect recovery of sensory function after nerve lesions, found that the onset of recovery is delayed and its progress slower after section of a nerve and that the degree of recovery is definitely less than after crushing. They observed an average rate of recovery of 1.98 mm a day after crushing the peroneal nerve and 1.57 mm a day after severing and suturing.

To test corneal sensitivity, a small cotton brush was used. A small piece of cotton was rolled between the index finger and the thumb, leaving its ends fluffy so as to make a small brush about 0.5 mm in diameter. The cornea was gently touched with the brush until a slight flattening of the tip of cotton was obtained, pressure on the cornea was avoided in order to eliminate misleading reactions. The testing should be done gently to avoid abrasions of the corneal epithelium and the possibility of infection, development of ulcers and opacification of the graft, such as occurred in 1 of my rabbits with a clear graft.

The cornea was divided into three zones for the purpose of exploring its sensitivity: (a) an area of 2 mm of the host cornea surrounding the graft, (b) the periphery of the graft and (c) the center of the graft.

The testing was begun on the second week after the operation and was repeated weekly for several months—in some of the rabbits for eight or nine months. All the rabbits were tested regardless of whether the transplant was clear or opaque.

It was found that the corneal graft was insensitive to the stimulus during the first few weeks after the operation, so that in some cases

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3 Castroviejo, R. Present Status of Keratoplasty, *Arch Ophth* **22** 114-126 (July) 1939, Keratoplasty, *Am J Ophth* **24** 139-155, 1941.

4 Gutmann, E., and Guttman, L. Factors Affecting Recovery of Sensory Functions After Nerve Lesions, *J Neurol & Psychiat* **5** 117-129, 1942.

the corneal suture was removed without tetracaine hydrochloride being instilled previously and without the slightest reflex being elicited. Moreover, this lack of sensitivity was also found in the 2 mm zone of host cornea surrounding the graft.

This status of sensitivity in the graft and the host cornea surrounding it has its explanation in the degenerative changes occurring in the nerves of the graft and the surrounding cornea, as shown in histologic preparations. There, alterations were in accordance with the analgesia following severance of sensory nerves, affecting not only the areas corresponding to the distal stump but a small area corresponding to the peripheral end of the central stump as well.

Recovery of sensory function in the clear graft became noticeable about the forty-fifth day after operation. In fact, on stimulation of the graft, a dull reaction was first induced in the form of a rather sluggish palpebral reflex. This corneopalpebral reaction became more active about the seventieth day, its final degree appearing to be less than normal, furthermore, it began to manifest itself at the periphery of the graft and remained more active there.

Recovery of sensitivity in the graft is a clear expression of nerve regeneration taking place in the graft. As a matter of fact, histologic sections showed the presence of new nerve fibers in the graft at the time a response to stimuli was obtained. This functional recovery gives no indication of the rate of reinnervation, since the latter takes place before any functional manifestation can be elicited. Maturation of the new axons occurs before return of function.

The physiologic tests performed show that the return of the corneal sensitivity takes place slowly. Considering the short distance involved in these experiments, the rate of recovery is low as compared with the rate of sensory recovery after section of the peroneal nerve<sup>4</sup>. In fact, the greatest distance through which reinnervation has to take place is 5 mm, assuming that recovery starts as soon as the nerves are cut and that it proceeds smoothly, it may be estimated that for recovery of sensory function after keratoplasty nine days is required for each millimeter of reinnervation.

After the rabbits were killed, the whole cornea, or the square piece of the graft only, was fixed for two weeks in a neutral solution of formaldehyde U S P (1:5). Frozen sections, 10 to 15 microns thick, were cut and impregnated with silver nitrate, according to the method of Gross-Schultze<sup>5</sup>. With this technic, the axis-cylinders stain black. With carmine used for counterstaining, the nerves stand out better on a pinkish background.

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<sup>5</sup> Mallory, F. B. *Pathological Technique*, Philadelphia, W. B. Saunders Company, 1938.

## STRUCTURE OF THE NORMAL NERVES OF THE CORNEA

The nerves of the cornea proceed from the fifth cranial, or trigeminal, nerve, the ophthalmic branch of this nerve divides into three branches to form the lacrimal, the frontal, and the nasociliary nerve the last one giving off the long ciliary nerves and the long, or sensory, root of the ciliary ganglion, from which the short ciliary nerves spring Long and short ciliary nerves participate in the nerve supply of the cornea<sup>6</sup> Nothing is to be added to the classic studies on the corneal nerves made by Dogiel,<sup>7</sup> Attias<sup>8</sup> and Hoyer<sup>9</sup>

It is established that from sixty to eighty nerve trunks penetrate the cornea at the limbus, at the junction of the posterior third and the anterior two thirds of its stroma<sup>10</sup> In addition to these large trunks, the superficial layers of the cornea at the periphery are innervated by the conjunctival, episcleral and scleral nerves in a triangular area

When the nerves enter the cornea, they are rather thick trunks formed by a variable number of nerve fibers, which are either dissociated and clearly seen or packed together in an even dark stem (fig 1)

The corneal nerves are oriented toward the center and the surface of the cornea Their diameter decreases gradually as they approach the corneal epithelium Soon after they have penetrated the corneal stroma, they give off a branch at an acute angle, from time to time new branches arise from the same trunk In time the branches give off secondary and tertiary branches by successive divisions

Besides the thick nerves, the corneal stroma has thin nerves formed of a single nerve fiber, they pursue a straighter course than the thick ones and have the same orientation Martinez,<sup>11</sup> in one of the most recent articles on the nerves of the human cornea, stated that in the stroma the nerves follow the lacunar system of the cornea, lying on the syncytium formed by the fixed cells of the stroma All the stromal nerves, through successive branching, crossing, lending fibers to each other or real anastomosis, form a wide plexus, the fundamental plexus Its constituent elements become increasingly thinner as they approach the epithelium Once they have reached the subepithelial region, they form by intercrossing, the subepithelial plexus, from which the epithelial nerves originate

6 Goldnamer, W W The Anatomy of the Human Eye and Orbit, Chicago, The Professional Press, Inc, 1923

7 Dogiel Die Nerven der Cornea des Menschen, Anat Anz, 5 483-494, 1890

8 Attias, G Die Nerven der Hornhaut des Menschen, Arch f Ophth 83 207-314, 1912

9 Hoyer Ueber der Nerven der Hornhaut, Arch f mikr Anat 9 220, 1873

10 Salzman, M The Anatomy and Histology of the Human Eyeball, Chicago, University of Chicago Press, 1912

11 Martinez, R Etude sur l'innervation de la cornee humaine, Trab d Inst Cajal d invest biol 32 75-109, 1940

The epithelial nerves consist each of a single nerve fiber, which has a rather straight course and becomes thinner as it nears the surface of the cornea. The nerves pass among the epithelial cells, at times penetrating their cytoplasm and coming in contact with their nuclei. They end in sharp points or in fine round or pearl-like formations.<sup>7</sup> Martinez<sup>11</sup> was not able to find these formations. Our observations agree with those of this author.



Fig 1—Normal cornea. Corneal nerve with simple plain division.  $\times 600$

As has previously been stated, the nerve trunks begin to give off branches soon after they have penetrated the cornea, usually after they have lost their myelin sheath. In general, they divide into two branches of different size (fig 1), more rarely into three branches (fig 2). The branching is at a more or less acute angle, however, from some single-fibered nerves a fine branch is seen to spring in T fashion. When a nerve gives off a branch, one of two patterns may be followed. Either the nerve fibers clearly separate into two bundles to form the new branch



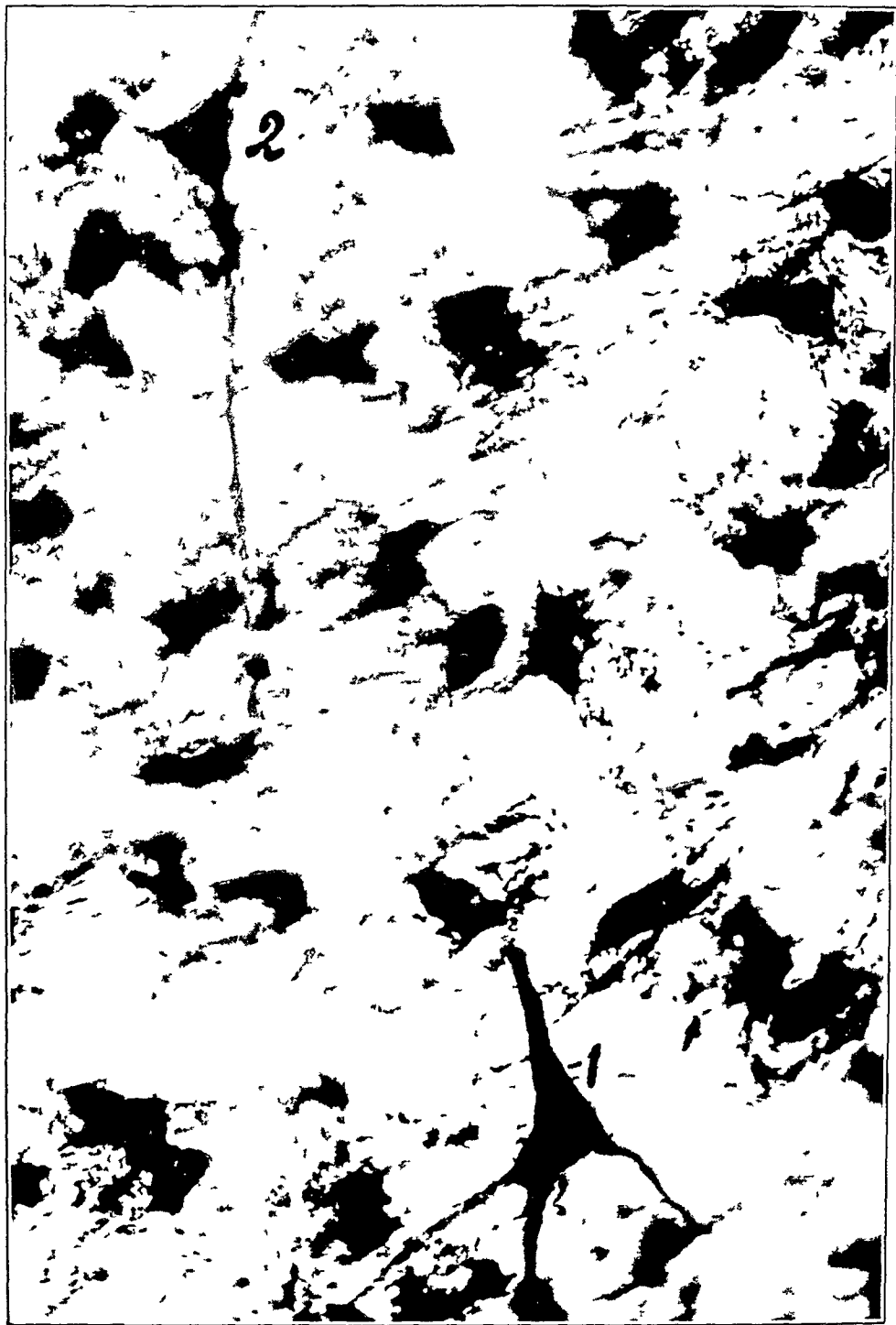


Fig 2—Normal cornea 1, corneal nerve with irregular plate at a three branch division 2 two branch division with triangular plate  $\times 630$

or some of the nerve fibers divide again at the same time, in the last event, the new nerve fibers are always thinner than the original ones. In most cases there is a dark-stained plate at the bifurcation of the nerve, 66 per cent of nerves show a plate, which frequently is triangular (fig 2), or more rarely round (fig 3) or elliptic (fig 4)

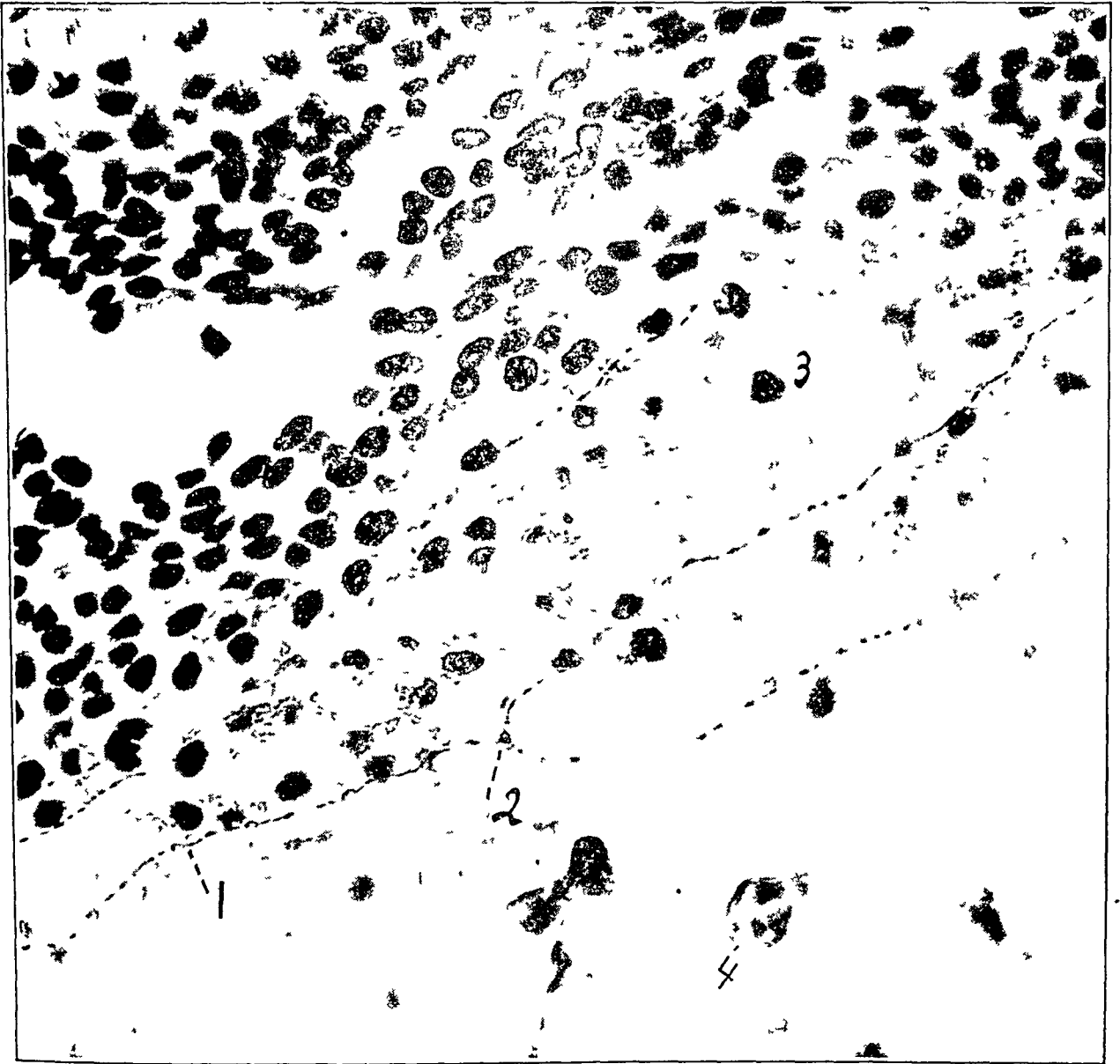


Fig 3—Normal cornea 1, epithelial nerve in the cornea, 2, branching nerve with round plate, 3, epithelial nuclei, 4, corneal corpuscle  $\times 730$

Occasionally, it is observed that when a nerve is broken, bridging fibers pass from one branch to the other, they do not come from the original trunk but arise from other nerve trunks and follow a retrograde course in the branch (fig 5)

When the nerves penetrate the cornea, each nerve fiber is formed of three elements (a) the sheath of Schwann, (b) the myelin sheath

and the (c) axis-cylinder<sup>12</sup> The majority of the fibers lose their myelin sheath about 0.5 mm from the limbus, before their first branching<sup>13</sup>, some of them, however, keep their myelin sheath for a longer distance. The axis-cylinders appear as black filaments with a uniform diameter, at the bifurcations, using the highest magnification, it is possible to see small, rather elliptic swellings. The diameter of the axis-cylinders is

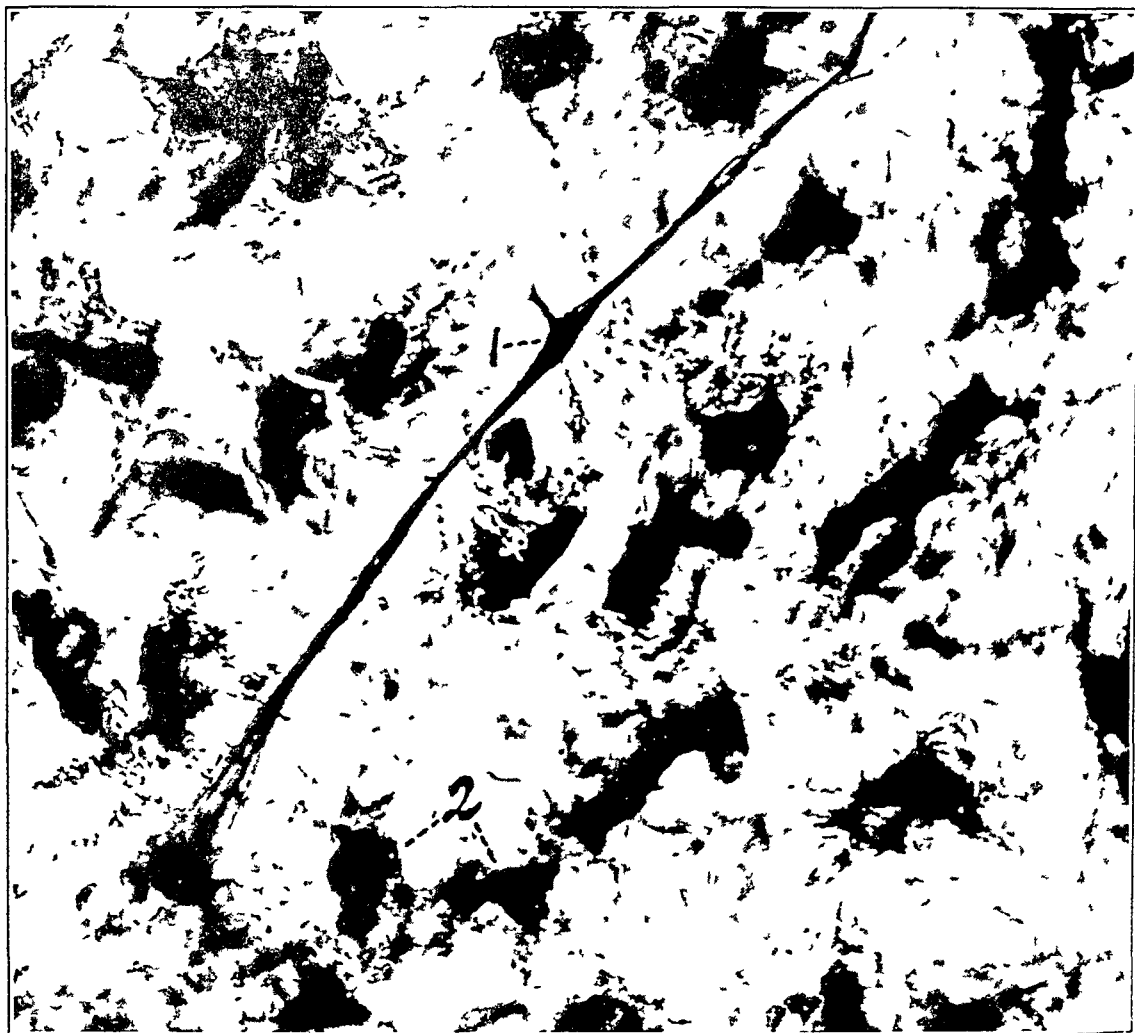


Fig. 4—Normal cornea. 1, corneal nerve with oval plate at a two branch division. 2, corneal corpuscle.  $\times 600$

not always the same. at the periphery of the cornea they are thicker than at the center, furthermore, in the same nerve some axis-cylinders are thicker than others in places having a ratio of 1.5 or 1.10.

<sup>12</sup> Bulliard, P. and others. *Traite d'ophtalmologie*, Paris: Masson & Cie, 1937.

<sup>13</sup> Wolff, E. *The Anatomy of the Eye and Orbit*, Philadelphia: The Blakiston Company, 1940.

Surrounding the axis-cylinders there is in the stromal nerves a clear halo with well defined edges, more easily distinguished in the single-fibered nerves (fig 6) This halo was described as a plasmatic sheath by Nageotte<sup>14</sup> and Martinez<sup>11</sup>, the former stated that it was defined by a sheath similar to the sheath of Schwann

Along the axis-cylinders, elongated nuclei are seen lying in the clear halo (fig 7), they have a clear nuclear membrane and round or taper-

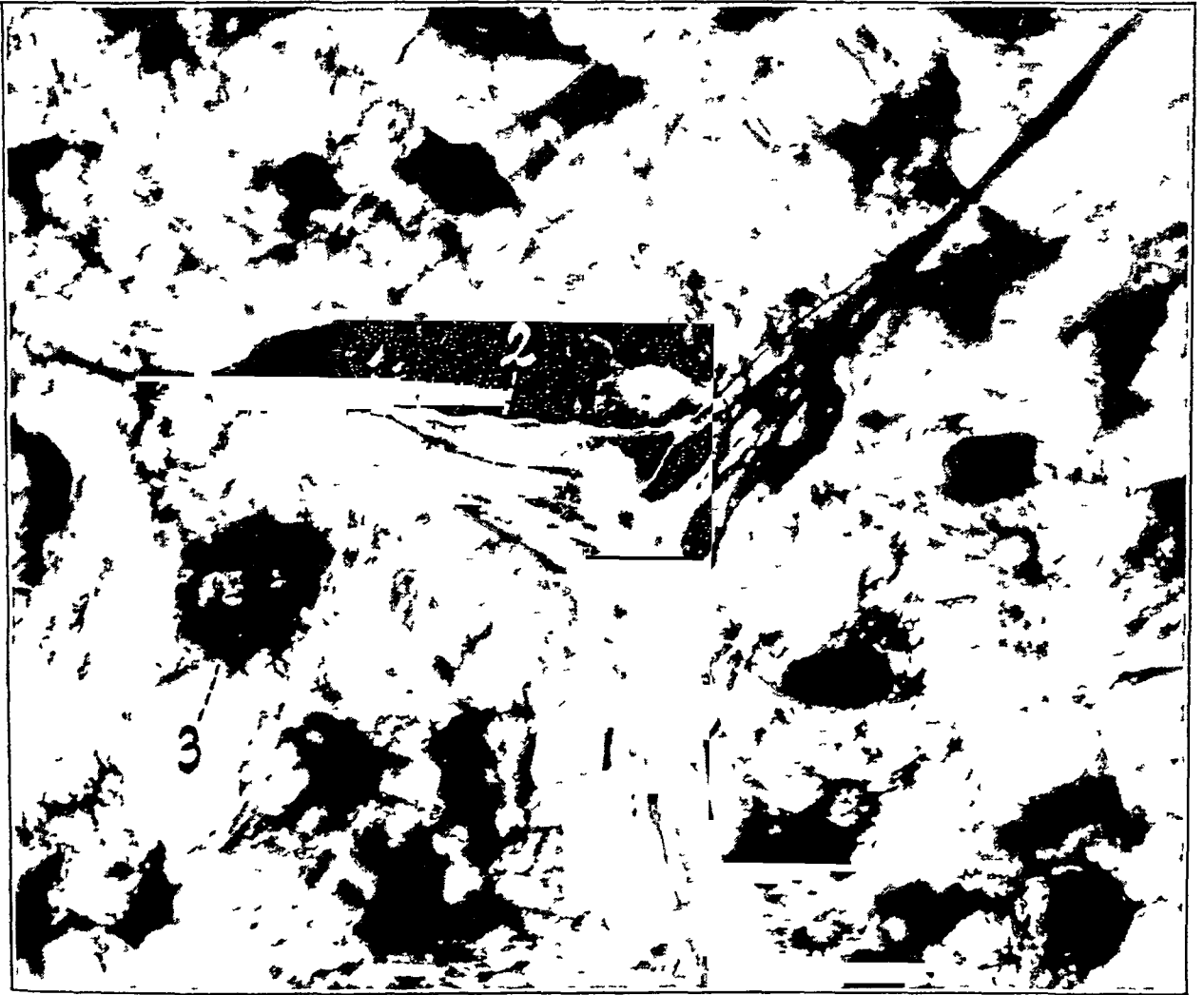


Fig 5—Normal cornea 1, large nerve with a two branch division, 2, bridging nerve fiber, 3, corneal corpuscle  $\times 600$

ing ends and contain a nucleolus and several round granules of chromatin It is clear that the morphologic character of these nuclei is much like that of the Schwann nuclei, and unlike those of the fixed cells of the

14 Nageotte, J Sheath of the Peripheral Nerves Nerve Degeneration and Regeneration, in Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932 (b) Nageotte, J, and Guyon, L Le syncytium de Schwann dans les plexus de la cornée ses connexions avec l'épithélium, Compt rend Assoc d Anat, 1926

stroma, which Boeke<sup>15</sup> considered them to be. In fact, this author also held that there was continuity between the nerves and the corneal elements.

It is evident that the halo occupies the space left by the disappearance of the myelin sheath and that it contains the Schwann nuclei. It forms a tubelike structure, the center of which is occupied by the axis-cylinder, and its contour is defined by a Schwann sheath.

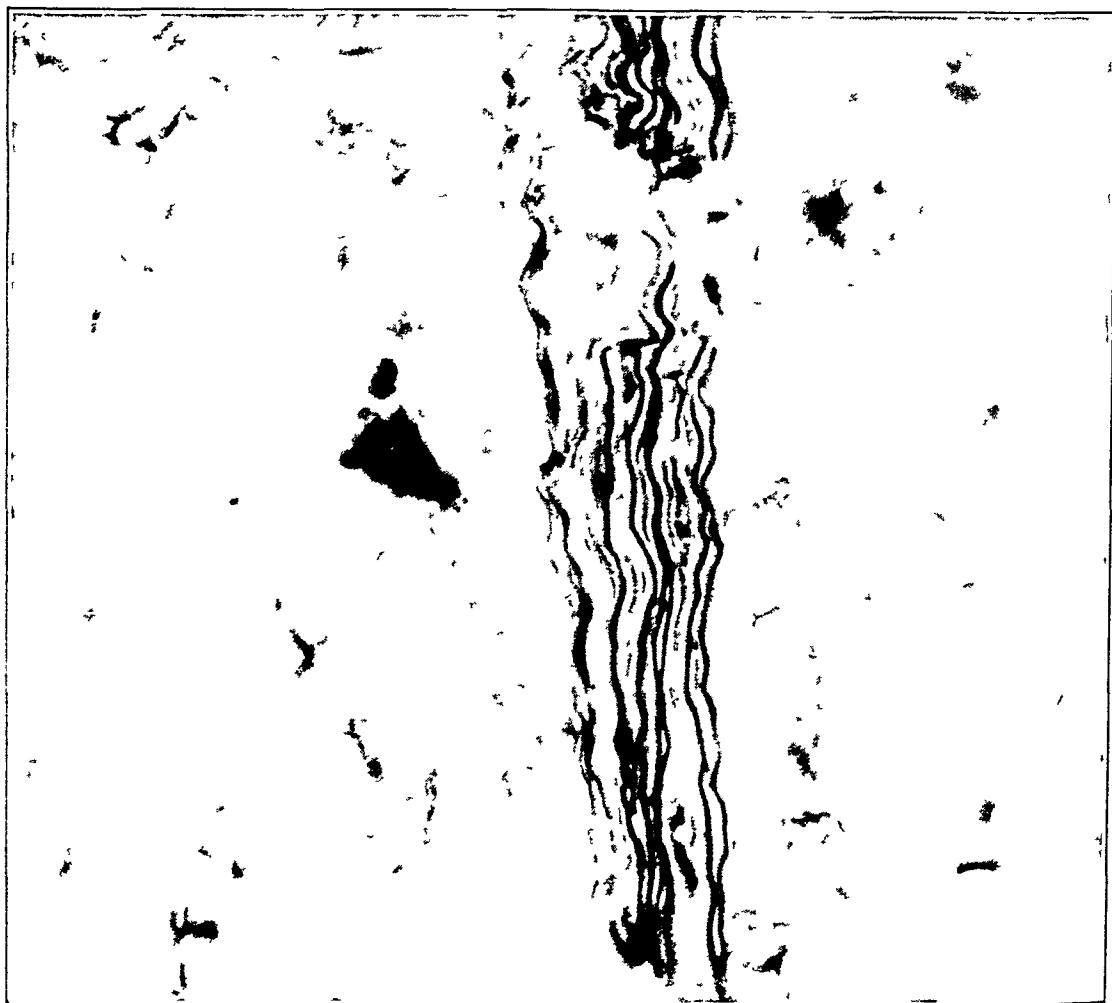


Fig 6—Normal cornea. Nerve with dissociated fibers and plasmatic sheath  
× 630

Characteristic features distinguish the epithelial nerves from the stromal nerves. The epithelial nerves are formed of single axis-cylinders, a striking feature of which is the presence of small, round beads along their course giving them a moniliform appearance (fig 3). On the other hand the axis-cylinders are naked, since no sheathing

<sup>15</sup> Boeke J. Die Beziehungen der Nervenfasern zu den Bindegewebelementen und Tastzellen, *Ztschr f mikr anat Forsch* 4 448-509, 1926

is detected around them In the epithelium, naked axis-cylinders come in contact with the epithelial cells

#### DEGENERATION OF CORNEAL NERVES IN VITRO

Degeneration of the nerves is a vital process, to study it in vitro, one should keep the nerves in the best living conditions According to Ramón y Cajal,<sup>16</sup> degeneration is a manifestation of life—once life

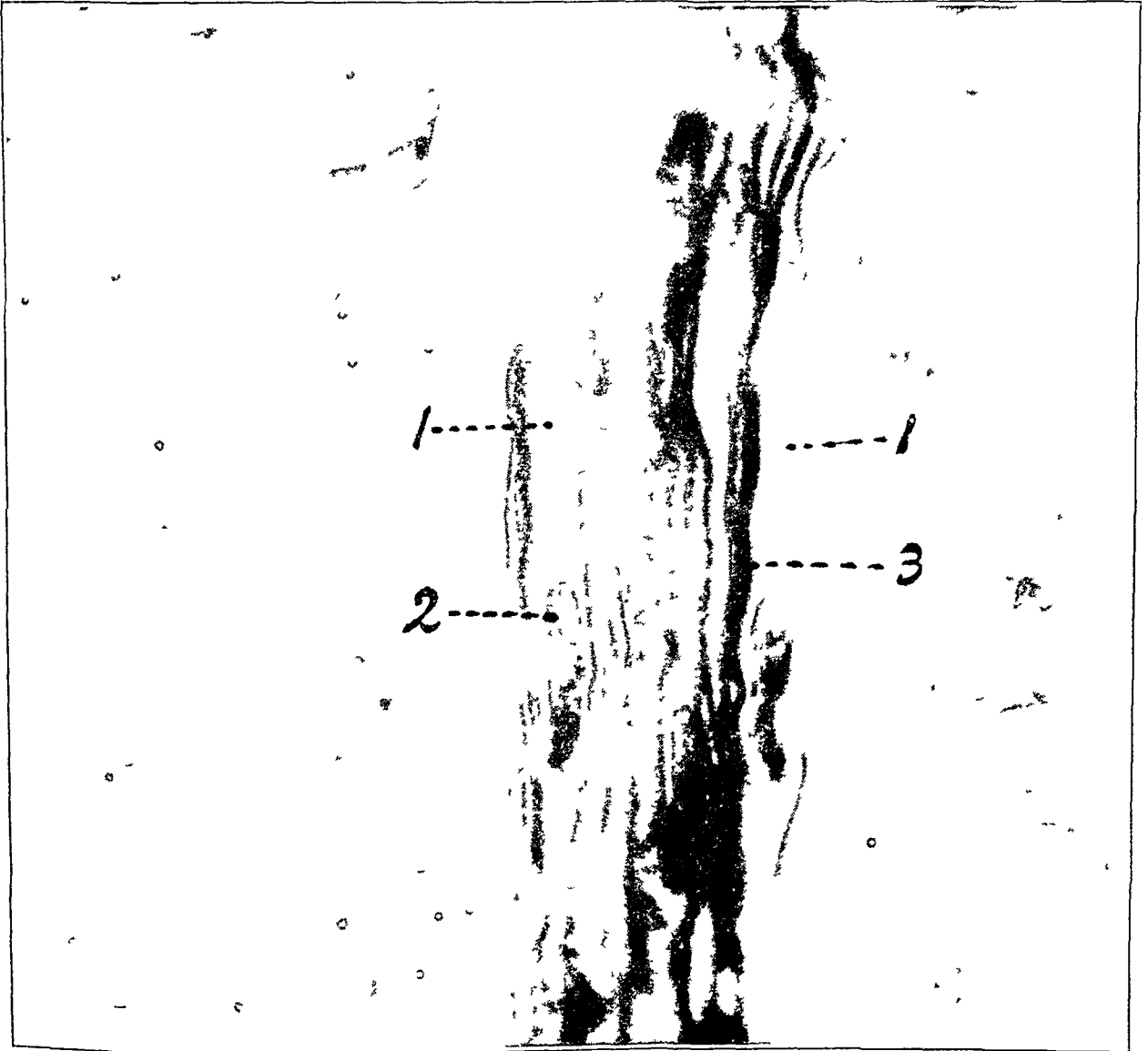


Fig 7—Normal cornea Nerve with (1) plasmatic sheath, (2) Schwann nucleus, (3) nerve fiber  $\times 1,260$

activities are paralyzed or putrefaction starts, the process stops Ingebrigtsen,<sup>17</sup> by culturing pieces of brain of chick embryos, was able

16 Ramon y Cajal, S Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928

17 Ingebrigtsen, R Study of the Degeneration and Regeneration of Axis Cylinders in Vitro, J Exper Med 17 182-191, 1913

to study in vitro not only the outgrowth of new axis-cylinders but their spontaneous degeneration after the fifth day or their degeneration after their severance

To study the degenerative nerve changes that might occur in the cornea in vitro, rabbit corneas were used. They were kept in two ways (a) in the moist chamber in Ringer's solution at a temperature of 37 C, and (b) immersed in Ringer's solution at a temperature of 2 C

In the moist chamber at 37 C the best living conditions were present for study of changes in the nerves. The pieces of cornea were kept there for periods of twenty-four to one hundred and forty-eight hours, after forty-eight hours the corneas became cloudy and edematous, and their thickness increased considerably, after one hundred hours being twice or three times the normal thickness of the cornea. Of these pieces of cornea, only those kept for twenty-four and forty-eight hours gave information concerning the behavior of their nerves. The pieces kept longer did not show any nerve structures, even when thicker sections were made and the silver impregnation was prolonged, probably because of the advanced stage of degeneration.

In sections of the twenty-four hour pieces, the abnormal condition of the nerves was immediately apparent. The fibers were separated from each other by edema. All the axons showed signs of degeneration, although not all to the same degree, one was first struck with the increased avidity of the fibers for the silver nitrate, presenting as they did, a dense, dark appearance, and with their diffuse hypertrophy. These changes were present in all the fibers, in addition to an increased tortuosity in the majority of them. Most of the axons were in the varicose stage of degeneration (fig 8, 1), with conspicuously thinned segments, alternating with somewhat tortuous, thickened ones. Some axons presented annular rings. These rings had a rather thick wall on one side and a very thin one on the other, their central space was clear and appeared empty, they seemed to be the result of an uneven longitudinal splitting of the axon (fig 8, 2). Some hypertrophied fibers were in a pregranular stage, their surface appearing as formed by a linear packing of granules (fig 8, 3). The finest fibers were in the granular stage but still kept a linear arrangement.

Besides the more or less uniform hypertrophy of the axons, fusiform swellings were seen along their courses. These axons had at irregular intervals pronounced strictures, which led one to consider them to be in a prefragmentation phase of degeneration, true fragmentation being present in occasional axons. A still more advanced stage of degeneration was present in some axons, which showed vacuolation, small, round clear vacuoles were alined along the axon.

All these changes in the axons set in and progressed with no appreciable reaction on the part of the nerve sheath and its nucleus, the

latter structures seemed to be indifferent to the regressive changes occurring in the axon

It could be inferred from the previous description that after twenty-four hours of incubation all the axons showed unequivocal signs of

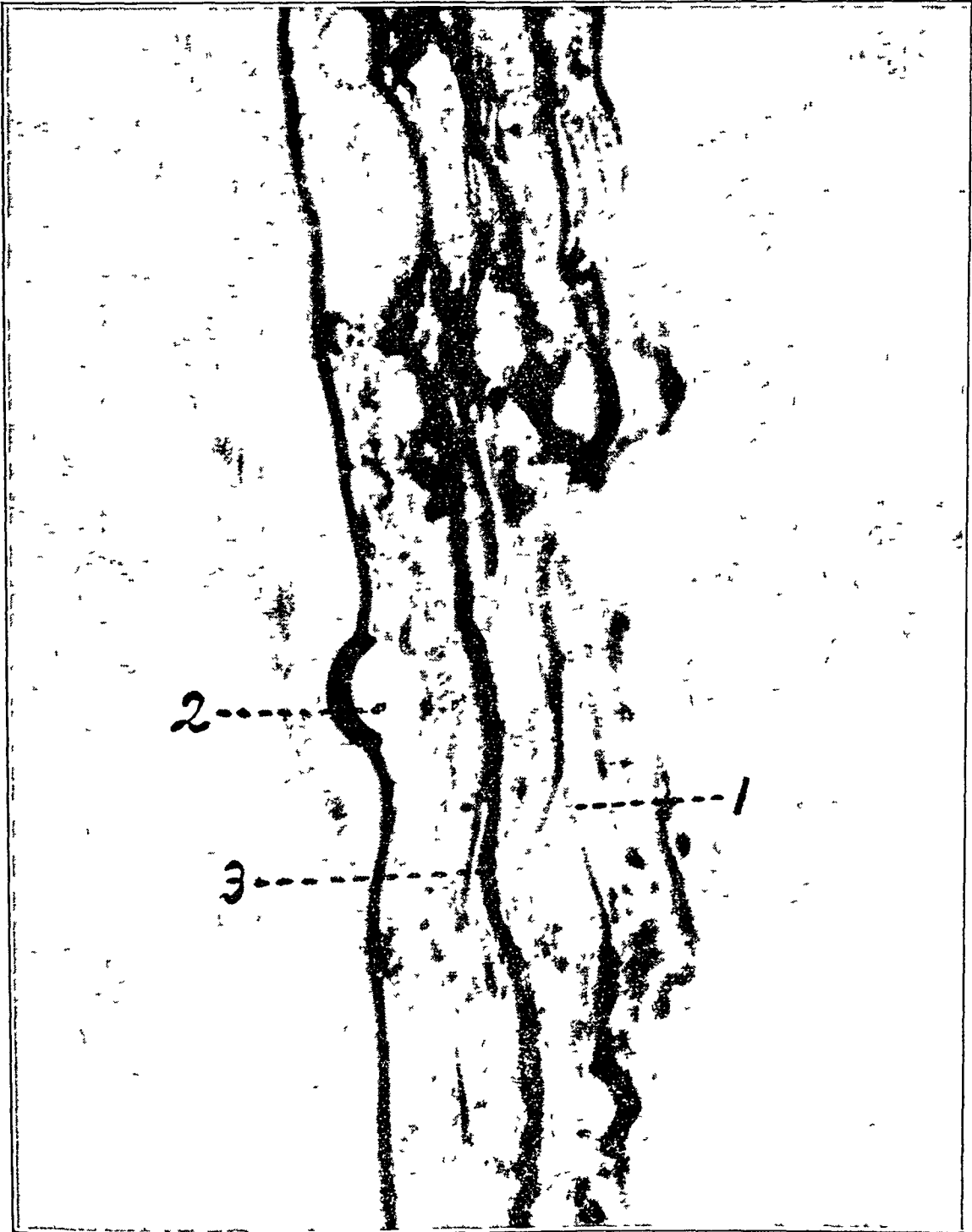


Fig 8—Flat section of a cornea kept twenty-four hours in the moist warm chamber 1, varicose stage of degeneration, 2, annular rings, 3, pregranular stage  $\times 1,260$

degeneration, ranging from simple hypertrophy to vacuolation and rare fragmentation, most of the axons being in a varicose stage It is note-



worthy that not all the fibers were equally liable to degeneration, the thinner ones showed the more advanced degenerative changes. This allowed us to see in a single nerve trunk fibers in various stages of degeneration. In no case were the least manifestations of regressive change observed in the Schwann elements of the axons.

The sections of cornea kept for forty-eight hours at 37 C showed the nerves in a more advanced stage of degeneration (fig 9). Most

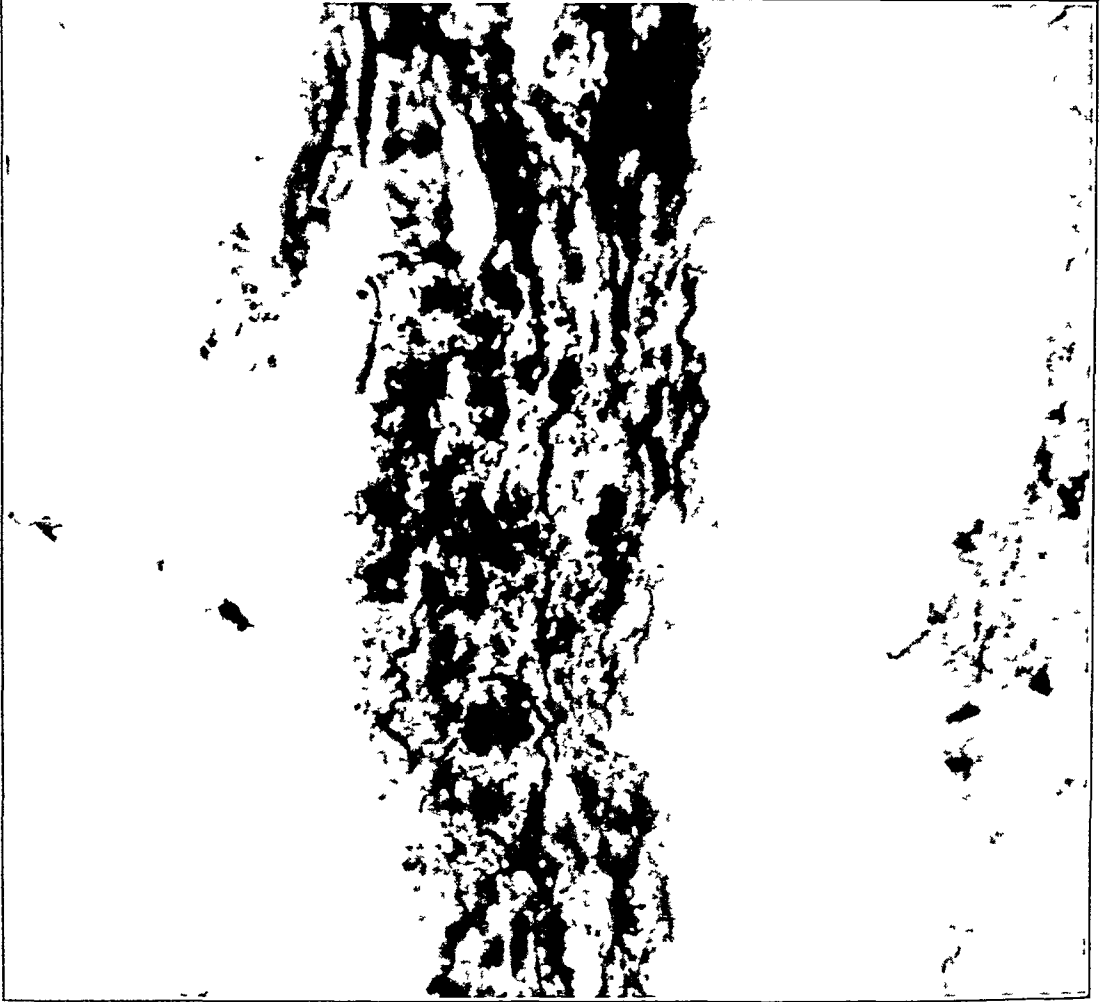


Fig 9—Flat section of a cornea kept forty-eight hours at 37 C, showing fragmentation and granulation of the axons. Notice the presence of clublike fragments.  $\times 630$

of the axons had lost their continuity, they were in fragments of various lengths with pronounced hypertrophy, which in some fragments was greater at one end, giving a clublike appearance.

The fragments were flexuous, some of them being coiled and arranged along the nerve tube or across it, most of them were in a granular stage, some still kept their continuity. Some sections showed

splitting and vacuolation of the broken axons. Besides these changes, the whole picture of the nerve was obscured by a diffuse granulation. The process of degeneration had gone farther in some nerves, most of their nerve fibers had disappeared completely, and the remnants were in the form of granulated axonic debris, scattered in the path of the nerve.

The corneas kept at a temperature of 2 C. were not in the best condition to study manifestations of living tissues. However, degenerative changes of a rather low grade took place. In fact, they started later and proceeded more slowly than in corneas incubated at 37 C. After the sections had been ten days at 2 C. the changes in the nerves corresponded to those observed in corneas kept twenty-four hours at 37 C. Most of the fibers showed, in addition to diffuse hypertrophy and increased avidity for the silver nitrate, a varicose stage of degeneration, some of them were in the granular stage, a linear arrangement being preserved. Fusiform swellings were seen and occasional fibers presented vacuoles and fragmentation.

#### DEGENERATIVE NERVE CHANGES ASSOCIATED WITH CORNEAL TRANSPLANTATION

When a corneal graft is cut, the corneal nerves are severed, and the nerves in the graft represent their distal stumps, these undergo wallerian degeneration, like that in the distal stump of any severed peripheral nerve. These secondary degenerative changes occur as the result of isolation of the nerves of the graft from the trophic stimulus that emanates continuously from the nerve cells of the corresponding centers. An important fact is that degenerative changes are also observed in the nerves of the host cornea in an area of about 2 mm. around the graft. These changes correspond to the traumatic degenerative changes that occur in the peripheral end of the central stump of any severed nerve, as the result of the direct action of the trauma.

The condition of the nerves in the graft and in the host cornea surrounding it furnishes the explanation of the anesthesia found in these areas. The earliest graft studied was that of a rabbit with a clear transplant which died as the result of diarrhea seven days after the operation. While the eye was being handled in the laboratory, the graft became detached, and only the graft was carried through the laboratory procedure.

The changes in the axis-cylinders were slight and limited to rare swellings and a manifest increased avidity for the silver nitrate. There were no interruptions in the continuity of the axons, however, some axons were in a pregranular stage. The plasmatic sheath surrounding the axons stood out more clearly and at places showed a fine dark granulation.

The degeneration proceeded rather slowly, so that on the twelfth day the number of swellings had increased. On the other hand, the changes had progressed more rapidly in the host cornea surrounding the graft. In the twelve day transplant, the host nerves in an area 2 mm in width had gone farther than those in the graft. The axons were extremely hypertrophied and of irregular caliber, with interruptions in their continuity and pronounced avidity for silver nitrate.

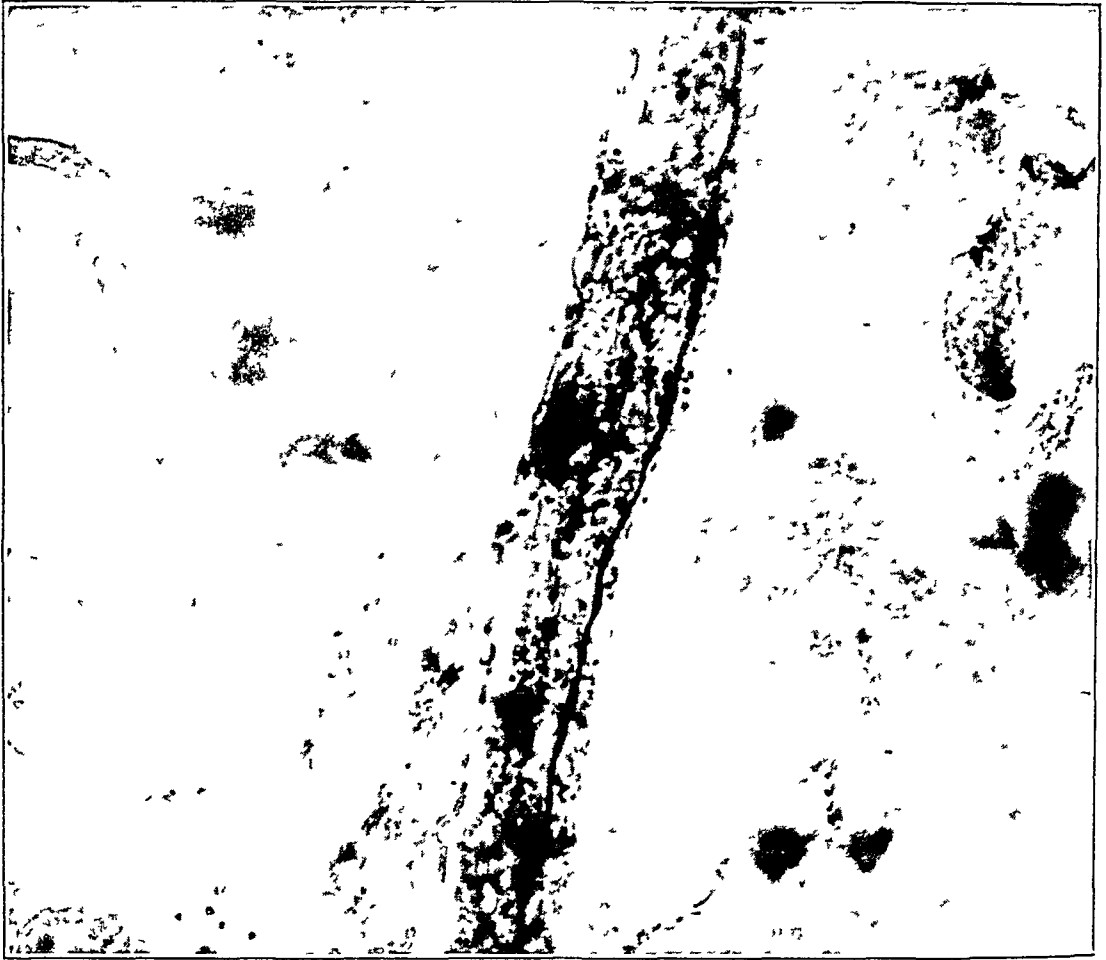


Fig 10—Flat section of a clear graft thirty days old, showing granulation and vacuolation of the axis-cylinders with a well preserved one  $\times 1,100$

The Schwann nuclei stained densely, and there was no indication of their proliferation.

In the thirty day graft, the degenerative changes were so advanced that, except for rare resistant axons, the majority were no longer recognizable (fig 10). The dominant feature here was the almost complete fragmentation and granulation of the majority of the axons. Many small, round, darkly stained granules were strewn in the path of the nerves, in places, they had a linear arrangement, as though the granu-

lation had just taken place. The most prominent detail was the presence of small, round, clear vacuoles, most of them were scattered irregularly within the nerve tubes, and some showed a linear arrangement.

In addition to these changes in the axons, the plasmatic sheath stood out clearly. The Schwann nuclei had undergone appreciable hypertrophy, with increase in the number of chromatin granules.

As was true of the degenerative changes in nerves observed *in vitro* not all the nerve fibers showed them in the same stage. This enabled

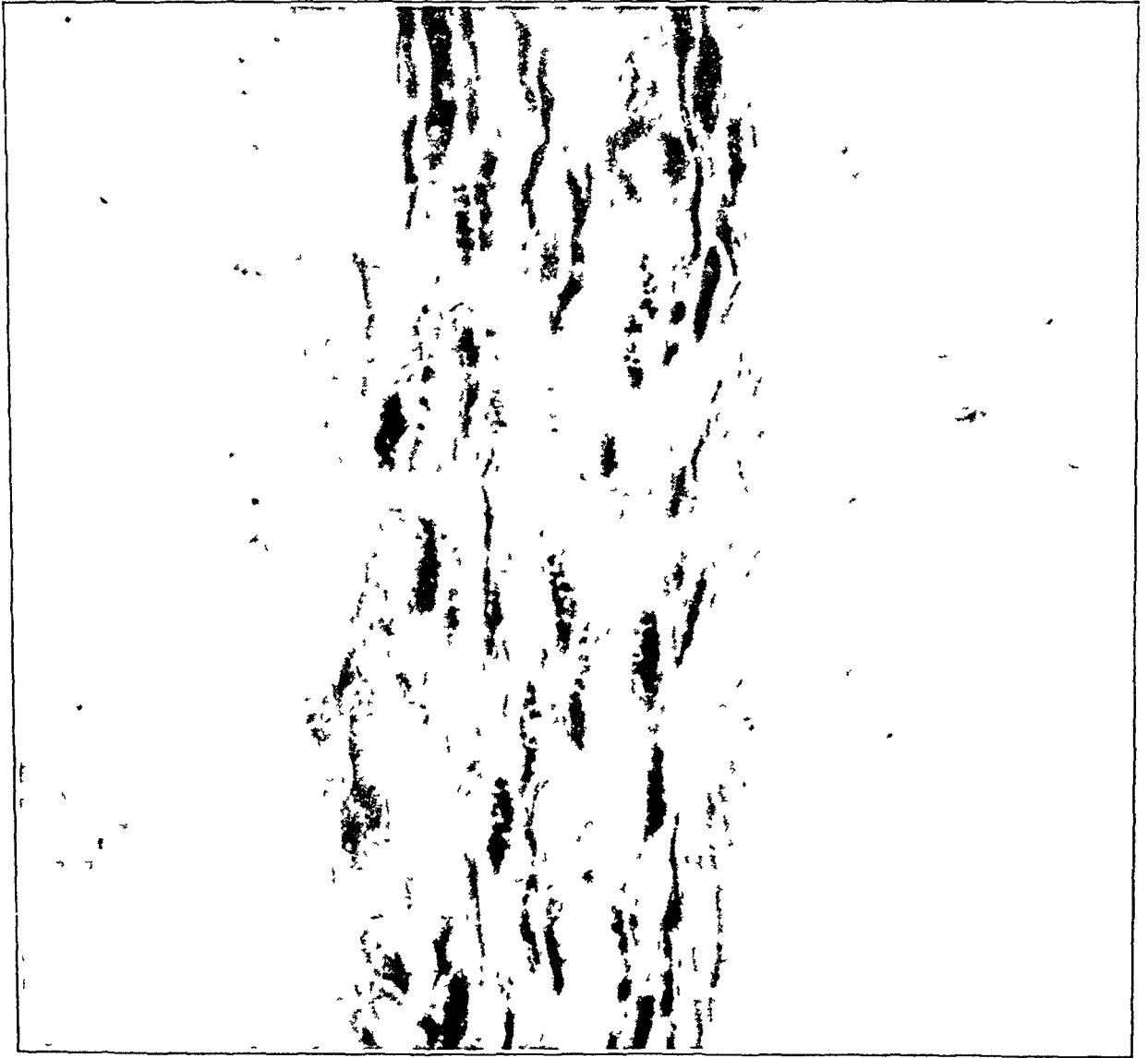


Fig. 11—Flat section of a translucent graft of one hundred and fifty-eight days. The axon-cylinders are reduced to small granular pieces.  $\times 1,100$

one to see, in addition to the advanced stages of degeneration, axons that had been broken down only into swollen, irregular pieces. There were rare axons which maintained their continuity but showed unequivocal signs of degeneration, such as irregularities in diameter with diffuse hypertrophy, localized fusiform swellings, increased tortuosity and greater avidity for the impregnating material (fig. 10).

The disintegration of the nerves increased gradually until complete granulation of the nerve fragments took place. Figure 11 shows a nerve in which the axons are reduced to small, granular pieces, most of them having disappeared.



Fig. 12—Flat section of a clear graft of sixty days. 1, Schwann nuclei, 2, aneuritic tube, 3, fine new axis-cylinder, 4, mature new axis-cylinder.  $\times 1,100$

These regressive changes in the nerves progressed until all the axonic debris had completely disappeared. In the sixty day graft, most of the old nerves were reduced to empty tubes, the axis-cylinders having disappeared completely. These aneuritic tubes had clear margins and were formed by the Schwann sheath and nuclei. Many of the

tubes were already occupied by thin, normal-looking axons, which had invaded the graft and represent the regenerating elements that grew out from the nerves in the surrounding host cornea (fig 12)

As stated previously in regard to the thirty day graft, not all the axons were in the same stage of degeneration. In fact, axons were still present in all stages of degeneration, although most of the nerves were reduced to aneuritic tubes or tubes that had been invaded by thin axons. The number of degenerating axons observed in the sections decreased gradually, and rare ones were still seen in grafts two hundred and seventy days after operation.

In addition to the axonic changes, there was moderate hypertrophy of the sheath, which showed the presence of fine granules. The number of Schwann nuclei had increased, and each nucleus was longer than normal, some of them were packed with many dark, round granules.

The degenerative changes in the host cornea advanced more rapidly than in the graft. Granulation and disappearance of the axons were completed here earlier than in the graft. In the sixty day graft, all the old axons were gone. No aneuritic tubes were seen. All the old nerve tubes were occupied by normal new axons, which, sprouting at the end of the normal host nerves, invaded the empty tubes (fig 13). The Schwann nuclei showed moderate hypertrophy and proliferation.

It is evident that in no section were macrophages noted. In the distal stump of peripheral nerves *in situ*, the removal of the axonic debris is accomplished by large numbers of macrophages. However, a role in this function has been attributed to the Schwann cells<sup>18</sup>. Since no macrophagic reaction takes place in the degenerating nerves in the corneal graft, one may assume that the disappearance of the axonic debris depended exclusively on its dissolution and elimination by the Schwann cells. The changes described proceeded somewhat more slowly in the opaque than in the clear graft, although not to a significant degree.

Similar changes occurred in the nerves of corneas kept in the warm moist chamber. *In vitro*, however, the phenomenon passed through all its stages in a shorter period. One might ask whether the process takes place faster *in vitro* or whether it is delayed in the corneal graft. Comparison of our observations with those of Weddell and Glees<sup>19</sup> for the cutaneous nerve plexus leads one to believe that degeneration of the nerves in the corneal graft is much delayed and proceeds slowly.

18 Ramon y Cajal, S. Histology, Baltimore, William Wood & Company, 1933. Weiss, P. The Technology of Nerve Regeneration. Sutureless Tubulation and Related Methods of Nerve Repair, *J Neurosurg* 1:401-443, 1944. Huber, G. C. Nerve Degeneration and Regeneration, in Stooly, D. Surgical and Mechanical Treatment of Peripheral Nerves, Philadelphia, W. B. Saunders Company, 1922.

19 Weddell, G., and Glees, P. The Early Stages of Degeneration of Cutaneous Nerve Fibers, *J Anat* 76:65-90, 1942.

## REGENERATIVE NERVE CHANGES IN CORNEAL TRANSPLANTATION

When a peripheral nerve is severed, the axis-cylinders in the distal stump die and disappear. The reinnervation of the empty nerve tubes is a function that has been established as depending on the proximal

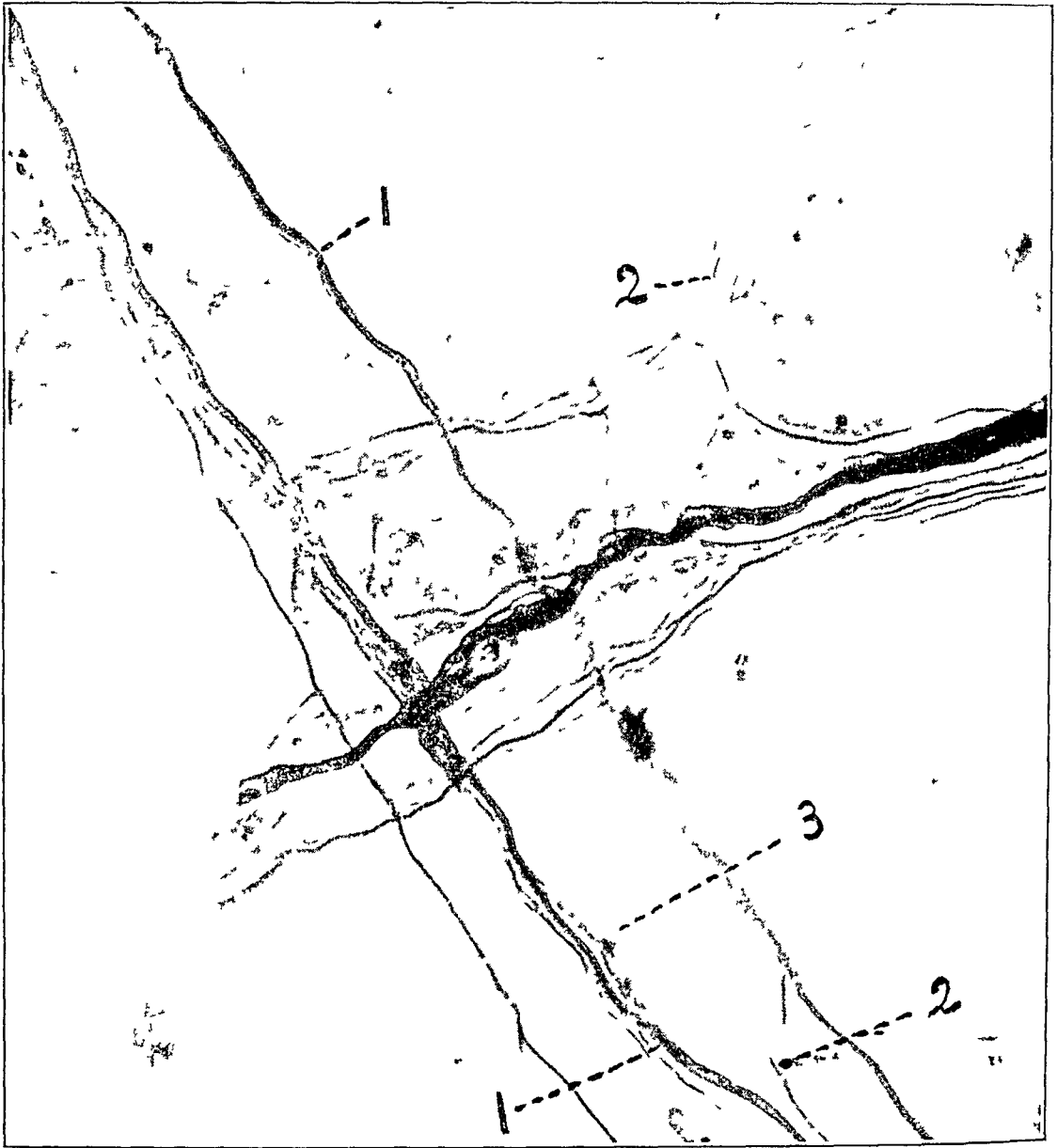


Fig 13—Flat section of the host cornea in a clear graft sixty days old 1, thick new axis-cylinder, 2, thin new axis-cylinder, 3, Schwann nuclei  $\times 1,100$

stump. In fact, the proximal stump of a severed nerve, through sprouting of its axis-cylinders, gives rise to new axis-cylinders (or axons) which invade the distal stump.

When severance of a nerve is followed by close approximation of its stumps, the newly formed axis-cylinders, having practically no

obstacle in their way, reach the central end of the distal stump quickly and penetrate it. When the two ends are not approximated, even though there is not extensive loss of nerve tissue, the down-growing axis-cylinders become dispersed in the scar tissue and penetrate the distal stump very slowly.

The new axis-cylinders are nonmyelinated, but soon they acquire a myelin sheath, which proceeds distalward. Myelination is a property of the neuron, although myelin cannot be produced except with the collaboration of the Schwann cells.

It is still a matter of controversy whether the Schwann cells precede or accompany the tip of the new axis-cylinders when these penetrate the scar tissue between the two stumps or any tissue deprived of nerve tubes. According to Weddell,<sup>20</sup> in most cases the Schwann cells grow first and the axis-cylinders follow them. Once the new axis-cylinders enter the distal stump, they find there the best conditions for their growth, the speed of growth being 3 mm every twenty-four hours.

Most of the studies on nerve regeneration have been made on the nerves of the limbs of dogs, cats and rabbits. The nerves have been either crushed or severed. Weddell<sup>21</sup> studied the axonal degeneration and regeneration of cutaneous nerve plexuses after crushing the main dorsal ear nerve of rabbits. Reinnervation takes place more quickly after crushing than after severance, it starts later and proceeds more slowly after severance. The presence of the first regenerating fibers in an organ means that functional recovery has started. Increase in number and caliber of the new axis-cylinders is necessary before functional completion is obtained.

In corneal transplants, as in the rest of the body, regressive nerve changes are followed by progressive ones, which eventually result in complete histologic and physiologic reinnervation of the corneal graft.

As stated previously, nerve degeneration was observed in the corneal graft and in the host cornea surrounding the graft in an area about 2 mm wide. These regressive changes proceeded more rapidly in the host cornea than in the graft. As a matter of fact, histologic preparations showed that the axonic debris had disappeared completely in the host cornea after sixty days (fig. 13). On the other hand, in sixty day grafts one could still see much axonic debris, which disappeared slowly. In grafts of two hundred and seventy days, rare degenerated axis-cylinders were still present.

The reinnervation of the corneal graft took place all around the graft. After traumatic degeneration of the nerves of the host cornea,

<sup>20</sup> Weddell, G. Axonal Regeneration in Cutaneous Nerve Plexus, *J. Anat.* 77: 49-62, 1942.

<sup>21</sup> Weddell and Glees<sup>22</sup> Weddell<sup>23</sup>



an outgrowing of new axis-cylinders began at the distal end of the nerves of the host cornea. These new elements were thin and fairly straight, with a uniform caliber, and took the impregnating material evenly. They sprouted all around in the host cornea and took a centrifugal direction toward the edge of the graft. These axis-cylinders were contained in the old nerve tubes.

This outgrowth of new nerve elements was evident in the second month after corneal transplantation. It seemed to proceed normally, and in the sixty day transplant one noted, in addition to the disappearance of most of the old axis-cylinders, the presence of the new ones. All the old nerve tubes in the surrounding host cornea were occupied completely by the new axis-cylinders (fig 13).

Figure 13 shows the condition of the nerves in the host cornea sixty days after transplantation. All the elements are represented here by new axis-cylinders, some of them have reached a diameter close to that of the normal axons, no empty tubes are seen, and the Schwann cells show practically no reaction to what is happening to the axons.

To enter the graft, these outgrowing axis-cylinders must pass through the organizing connective tissue already present at the line of junction of the graft and the surrounding cornea. Here the absence of open pathways creates an obstacle to the tip of the fiber, against which it must struggle. This obstacle exerts a manifest action on the growing tip. First, it is a retarding effect, in fact, the growth proceeds very slowly through scar tissue. The denser the scar, the greater is the obstacle opposed to the outgrowing axon. Second, the regular arrangement of the axis-cylinders is lost, and they take an irregular course. It is supposed that most of the fibers are preceded by the Schwann cells, which lay down the tracks for the axons. When the regenerating axis-cylinders reach the scar, they take a wavy course, though they still keep an orientation that has the grafts as its goal. Some fibers undergo a 90 degree bend and run along the edge of the graft. It is interesting that at the scar, when vascularization of the graft takes place, some axons take the path of least mechanical resistance by following the course of the vessels (fig 14).

The new axis-cylinders invade the corneal graft, reinnervate it and restore its sensitivity. In the forty-five day graft, one begins to obtain some response on stimulation of the graft. Histologic sections of these grafts revealed the presence of occasional fine new nerve fibers. Reinnervation at this stage is a demonstrable histologic fact. It indicates that invasion of the graft by the new axons has started earlier, apparently after the thirtieth day. Sections of thirty day grafts showed active regressive changes without the least suggestion of new axons.

In the sixty day graft, disappearance of the old axis-cylinders was well advanced. The main feature of these sections was the presence

of new axis-cylinders. These were represented by fine, evenly impregnated threads of a uniform diameter (fig 12). In addition to the fine new elements, some had reached a certain degree of maturation, they were thicker and more densely impregnated.

The majority of the new axis-cylinders were contained in the Schwann sheaths left empty by the disappearance of the old axons.

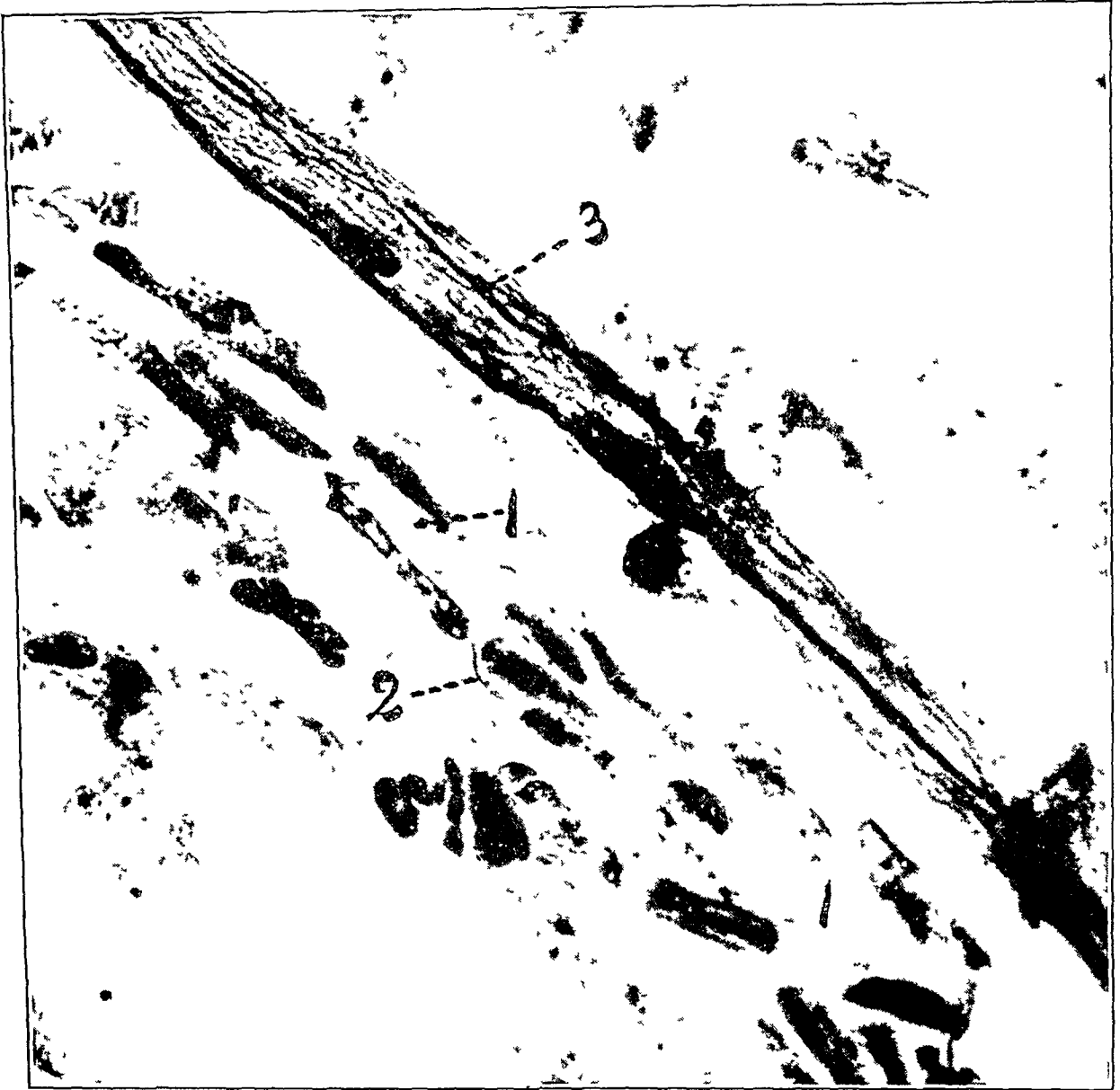


Fig 14—Section of a clear graft sixty days old. 1, blood vessel, 2, fine nerve fiber, 3, nerve following course of the blood vessel.  $\times 1,100$

However, some of them were naked and lay in contact with the stromal tissue of the graft (fig 15).

Not all the Schwann sheaths were occupied by the new elements, a number of them were empty tubes, filled with an increased number of Schwann nuclei. These tubes had a clear margin. The Schwann nuclei

that filled them were more numerous and larger than normal, they retained their normal elongated shape. When the tubes had been invaded by the new axis-cylinders, the Schwann nuclei were arranged along their course.



Fig. 15—Flat section of clear graft of sixty days. 1, naked nerve fiber, 2, sheathed nerve fiber, 3, corneal corpuscle.  $\times 1,100$

Neurotization of the graft proceeds gradually. At the same time that the number of regenerating axis-cylinders is increasing, maturation takes place. Maturation consists in a realignment of the Schwann nuclei and an increase in the caliber of the axons.

Figure 16 shows a section of a translucent graft of one hundred and fifty-eight days. Here, an old nerve tube contains, besides a still degenerating axis-cylinder, three new axons which have reached a certain degree of maturation. At the same time, the number of Schwann nuclei has increased. Thus, the appearance of the new nerve elements is fairly normal except for slight reduction in their diameters.

Comparison of these changes in the clear, translucent and opaque grafts showed practically no difference in the process of reinnervation.

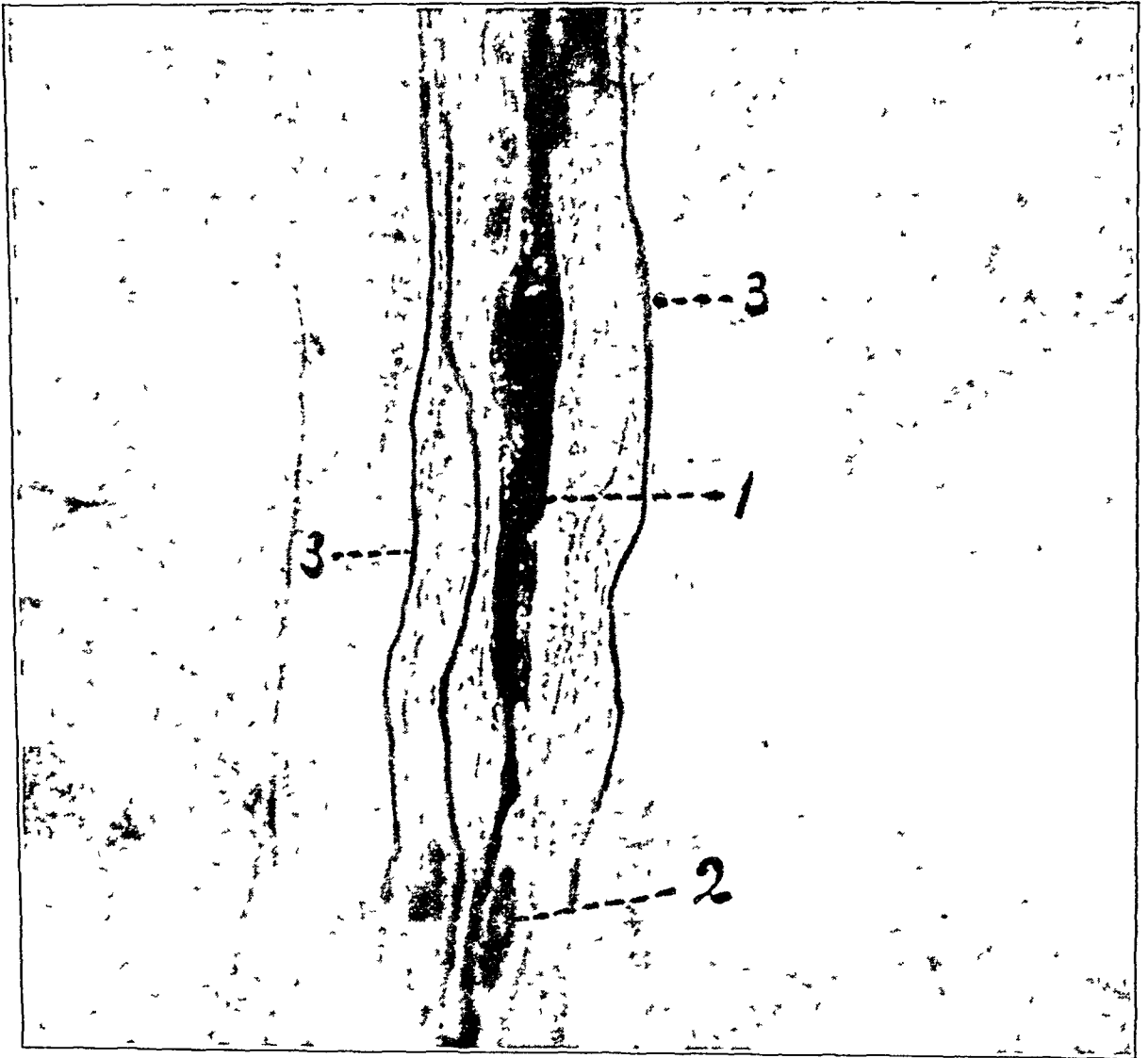


Fig 16—Flat section of a translucent graft of one hundred and fifty-eight days  
1, old degenerating axis-cylinder, 2, Schwann nucleus, 3, new axis-cylinder  
× 1,100

except for slight retardation in the maturation of the axons in the opaque graft.

There is in the corneal graft an important factor that changes the conditions under which reinnervation takes place. In most of the experimental work on nerve regeneration, the process has been studied

after crushing or severing the nerves. The outgrowing neuraxes, after crossing the crushed area or the scar tissue between the stumps, penetrate the old, empty nerve tubes. In the case of the corneal graft, the nerve ends are far from being approximated. When the new neuraxes reach the graft, most of them find no preformed pathways to facilitate their growth. The stroma of the graft continues to present an obstacle to the outgrowing tip except when the axons penetrate the old tubes.

Reinnervation of the graft is governed by factors other than merely the impulse to growth (*vis a tergo* of Held). Orientation of the axons toward the center of the graft cannot be explained by contact. There seems to be a factor that guides the new neuraxes toward the aneuritic tubes and orients them to the center of the graft. These empty tubes, in addition to the supposed chemotropic action exerted on the growing neuraxes, represent the pathway of least mechanical resistance. The absence of nerves in the graft seems to stimulate the surrounding nerves to grow. Obviously, retarding factors slow the progress of reinnervation in the graft. In fact, a few fine new axons are first noticed in the graft approximately on the forty-fifth day. In the sixty day graft, besides fine new axons, some axons have reached a higher stage of development. Maturation of the new elements, as well as increase in the number of axons, continues slowly. Sections of grafts of nine months show fairly normal-looking nerve fibers.

In tests of corneal sensitivity, a dull response to stimulation of the surface of the graft appeared on the forty-fifth day. From this point, the corneal sensitivity increased until an anergic corneopalpebral reflex was obtained on the seventieth day.

From the histologic analysis, it is apparent that the graft was invaded by the regenerating axis-cylinders a few days before any physiologic response could have been elicited. Apparently, a certain degree of maturation and saturation in nerve supply is needed before a response is obtained. This latent period between anatomic and physiologic recovery has been found in general to be longer after severing than after crushing a nerve.

Maturation of the regenerating axis-cylinders conditions the progress of sensory recovery until functional completion is gained, which has a threshold lower than normal.

#### CONCLUSIONS

From the experimental work, the conclusion is reached that the corneal nerves behave like any peripheral nerve after its severance. The corneal graft shows regressive changes followed by regenerative ones.

When the cornea is stored in Ringer's solution at temperatures of 2 and 37 C, respectively, the nerves undergo a process of degeneration, which passes through the usual stages. Degeneration takes place more

rapidly at 37 C, its rate being about the same as that in the distal stump of any severed peripheral nerve

In cases of corneal transplantation, degenerative changes develop in the nerves of the host cornea and of the graft. In the host cornea, the nerves degenerate in an area 2 mm wide around the graft, these changes are the result of direct action of the trauma exerted on the nerves by the cutting instrument, they follow a course more rapid than that in the graft itself.

In the graft, the nerves represent the distal stump of the severed corneal nerves and undergo wallerian degeneration. These degenerative changes have a rather delayed onset and progress very slowly, more so than in the distal stump of any severed peripheral nerve. They go through the same stages as those in the stored corneas, though the degeneration is still slower than that in corneas kept at 0 C.

The cornea being an avascular tissue, the corneal graft is not under ideal nutritional conditions. This apparently determines the retarded onset and slow course of nerve degeneration in the graft and the absence of macrophagic reaction.

Reinnervation of the graft is accomplished by new nerve fibers which sprout from the nerves of the host cornea all around the graft. These new fibers, passing across the scar at the junction of the graft and the host cornea, invade the graft and reinnervate it, restoring its sensitivity. Physiologic tests of the graft begin to yield a response forty-five days after the operation, the intensity of this response gradually increases but never reaches the normal threshold of corneal sensitivity. Nine months after operation, the sensory recovery has not yet reached the normal level.

Histologic study of the grafts revealed, on the forty-fifth day after operation, the presence of fine new axis-cylinders, which gradually increased in number and diameters, without reaching the normal fiber size.

It is evident that reinnervation takes place before a response to stimulation of the graft is obtained and that a certain degree of maturation of the new axons and saturation by the nerve supply of graft is necessary before a response is obtained. The improvement in the sensitivity of the graft depends on the increasing innervation and on the size of the fibers.

A comparative study of clear and opaque transplants shows no significant differences in the status of the sensitivity of the graft and in the morphologic features of their regenerating axis-cylinders.

Dr J. L. Rodriguez Candela selected and modified the method of silver impregnation used in this work, and Mr. Max Gonzalez assisted in making the sections and stains.

## TESTS OF DEFECTIVE COLOR VISION

Reflections Based on Experience in Testing Persons With Defective Color Sense

BURTON CHANCE, M D

PHILADELPHIA

“COLOR,” in the past ten years, has occupied with increasing intensity the minds of physicists and physiologists, as well as the military forces of the land sea and air and industrial managements, in the effort to clear up its mysteries and to apply the knowledge obtained to useful ends. I wish to give an account of my own interest in the subject.

From my earliest years I have been interested in the “color vision” of both man and animals, even before I began to go to school. I observed that some persons who visited my home were unable to distinguish the colors of the objects about the house with the acuteness manifested by my brothers and sisters.

One striking instance repeatedly confused me. Two brothers, connections of my mother, captains of sailing ships, on their visits to us after voyages, annoyed me by their insistence on declaring that the colored objects which I offered to them were of another color than that which I had called them. My brothers, sisters and I were given small cards to register our attendance at Sunday school—four red ones for the weeks, to be exchanged for a green one to denote the month’s regularity. One uncle, especially, aroused my indignation by insisting that I had not earned the green card because it was of the same color as the others, yet, as young as I was, I noticed that he was equally uncertain that the red cards (which were of a rose tint) were red. The other brother, the elder, would agree with him, but avoided disputing with us, yet he was uncertain that my maltese kitten was as gray as I maintained it to be. Being the youngest in the family, I was forbidden to dispute further. Now, these two men were expert seamen, they had run their ships during the “blockade” in the Civil War period. Later, when stringent pilot regulations were enforced, these competent sailors were refused licensing. The son of one took over his father’s ship. He was a headstrong youth, who counted himself more efficient than his father, for had he “not qualified himself

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Read at a meeting of the Section on Ophthalmology of the College of Physicians, Philadelphia, Dec 19, 1946

as navigator?" But he lost the ship on his third voyage out. Now, all the male members of those two families, who were intimate associates of our family, when they visited us, appeared in garish colors and seemed to lack something, yet I could not understand what it was that affected them. They would not admire the colored prints shown them. At that time, also, a Negro house servant, of whom we children were fond, could not properly sort our colored garments when they were returned from the laundry.

In my first school days, as the classes were being taught the colors and color mixings, I noticed that boys who hesitated in their naming of colors also made funny mistakes when they were directed to mix them or to define colors complementary to those called "primary."

So it happened when, years later, men were sent to me from the railroads and other transportation services, the marine and the air, I became impressed with the outward appearance of those with defective color vision and the likelihood of detecting color deficiencies even before I made ready to "test" them.

In attempting to solve the problems as they presented themselves, I, like Sir Isaac Newton, have been on my knees struggling "to count the piles of stones which I had gathered on the seashore."

A normal visual acuteness enables a person to act speedily and unmistakably, even when unable to give the accepted names of tints or shades. I try to avoid suspecting the ability of one who declares he is "color ignorant." Once I was given the opportunity to test the sensitiveness of a group of mentally subnormal children. All had had kindergarten courses but were not fit to enter the primary classes. They had had experience in matching colored papers and strings, and none was found deficient in color vision, lamp lights and wools were rapidly disposed of by them. One day, after 2 of these boys had been examined, an old, long-experienced railroad engineer failed dismally in naming the lights correctly.

In recent years I have been greatly concerned by the much advertised attempts to correct, if not cure, so-called color blindness. In my judgment, faulty color perception is due to a congenital absence of power, as distinct a defect as are the congenital marks in a malformed eye. All attempts to relieve or to remove the visual defect are specious and bogus. The optical structures of the ocular system contain no elements for the correction of such an aberration. Such persons, however, can learn to memorize the colored plates put out by the Japanese and German observers, so that the correct naming of the plates might be accepted as qualifying them for the passing of service tests, but in actual service, when wrapped in fog and darkness, they are bound to miss out.



Sometimes I have been skeptical of the complete ability of particular observers who in times gone by have advocated certain forms of tests, and I have suspected that their own color sense was defective. Certain persons may be insensitive to red and yet have otherwise excellent color vision, and others seem to have normal sensitivity to red.

From my experience, in spite of what may already have been declared to the contrary, I am convinced that to a distinct, yet moderate, degree "color blindness" can be acquired in adult years. Chewers and smokers of heavy strong tobaccos, especially those who drink freely of the cheaper alcohols, have manifested difficulties in color vision, their responses, however, are not such as are shown by persons with so-called red-green blindness. Their general visual acuteness, both direct and peripheral, has been found very defective. But when they were abstinent and continued under medical treatment, distinct power of color vision was restored to them particularly those who were "rheumatic" or syphilitic. Abnormalities in color vision have been found during the course of influenza and have disappeared on recovery. Various drugs may affect color perception, thus quinine has produced inequalities in green vision and disturbance in the general threshold of color vision. Colors may appear different in daylight and in artificial light. As age advances, changes in the crystalline lenses may affect sharpness of perception.

Color vision tests are not of value as tests of mentality. In some of the Navy examinations, especially, bright youths were much slower in responding and in selecting the skeins, and other objects, than were the subjects of a lower mentality.

It has been accepted that female subjects rarely manifest "color blindness," a statement which may be true, for I have not been consulted by complaining women. In the first world war, however, there was sent to me a detachment of women applicants for Army nursing. All were professionally qualified, but were beyond the age of nurses who had been accepted for the first expedition. As I sized them up, having still my prejudices, based on appearance, I was little astonished to find that 30 out of 48 examinees were unable to match the sets of the Holmgren and the Williams skeins which had been issued, they fumbled and hesitated in quite the same manner I had observed in defective men, and, although their selections were similar to those usually made by male examinees, they were not so decisive or the distinctions so pronounced. Accordingly, I could "not recommend that they be employed in positions necessitating the recognition of colored signals." In spite of the report to the Board, the women were accepted for the usual occupations of nurses, but were not sent overseas.

In my attention to suspect subjects, I have proceeded exactly as in the routine ophthalmologic study of all persons consulting me. In making

up the reports, other details were noted as having been observed. Perimetric outlines commonly varied were quite unlike those obtained in cases of retinoneural disturbances due to causes other than those dependent on deficient color sense. It might be that the responses in the perimetric tests denoted not the perimeter colors but the recognition of the presence of the targets.

Comprehension of color blindness and indeed, the normal perception of color, involves physiologic and psychologic as well as physical factors.

While it is true that the wool tests are somewhat outmoded I have detected with these tests many a youth with defective color vision particularly those who had learned all the German and Japanese charts. The replies of the subjects in selection of the skeins were illuminating and of value in all considerations. Beginning with the old Holmgren set, with the standards rose green and red the examination was followed with the Williams set with its greater number of wools, finally the William Thomson stick was employed because of its simple accuracy. All the skeins selected were carefully recorded and the examinee was given the privilege of reviewing what he had selected, when he insisted, he was given another trial, or as many as he desired until convinced that his color sense was defective. By that time he had become so confused, and his visual memory so exhausted that his condition was readily apparent to all. It is remarkable that serious errors can be made on a simple stick consisting of only forty skeins, as devised by Thomson the test being the result of his laborious studies extending over twenty years. For a long time he kept carefully wrapped and noted the myriad of skeins chosen by the examinees, from which he contrived the row of standards and the faulty skeins. Scores of the packets were preserved by him and later came into my possession, from these his decisions might have been confirmed.

I wonder what the bees' color sense might be. In following the bees in my garden during several successive years, I was impressed with the insects' steady visits to the color which I noticed their first choosing. The variegated clumps of vivid phlox offered a good field for observation. By dawn the honey gatherers might be seen already on their tours, and, as they started out so did they continue to visit the flowers of the one color they were first seen to approach. If a white flower was first visited, only the white ones were sought throughout the tours, moreover, the bees would confine themselves to one kind of plant. Bees visiting the flowers of other colors likewise maintained their distinct choice. Bees visiting other varieties of plants kept their chosen colors as distinctly as did those visiting the phlox. No other varieties of insects maintained such a limited choice as did the bees, it was the wasps, ants and flies which caused crossing of the

pollens—to the extent that in the next season my much desired colored flowers became dull and mixed. In my observations, I had no means at hand of sequestering a bee so that I might see what it would select on its next departure from the hive. I could not seduce the bees by honey or sweets spread near the flowers, they all seemed to be impelled to pursue a definite plan of tour.

Color perception must be an intellectual manifestation of sentient animals, yet I have doubted whether the dog's mental selection of colored objects can be so much for the color, as though the color were "consciously" known to him, as for the sense of smell. All have marvelled at a dog's recognition of persons at remarkably great distances, and of the occurrence of incidents beyond limited human perception.

Thus far I have been speaking of my personal experiences. I am still at Newton's feet "counting the pebbles", daily as I pay homage to the small engraved portrait of him that hangs on my walls. I wonder whether I can ever understand the mysteries of the science of color vision. After forty odd years of reading and endeavors I am alas, still in darkness.

What is "color"? What is that which transfixes one by the sensation produced in the eye by the rays of a decomposed light? It has no synonym and the lexicographers have had difficulty in defining it. Webster gives this definition: "A quality of visible phenomena, distinct from form and from light and shade depending upon the effect of light of different wave lengths on the retina."

Color is not a material substance, it is a sensation perceived by the eye and is generated by waves of light emanating from an object whose image is projected to the eye. All waves have not the same frequency, and it is the variations in these frequencies which give rise to the various colors. Other light waves have been estimated to have a frequency as great as 20 000 000 000 to 40,000 000,000,000 per second. Each color has its own frequency. In the rainbow or the prismatic spectrum the range extends from the red end of about 390 000 000 000 vibrations per second to the extreme visibility of violet, of about 750 000 000 000 000 vibrations per second. Between these two ends of the spectrum, the human eye is capable of distinguishing orange-red, orange, orange-yellow, yellow, green, green-blue, cyan blue, blue, violet-blue and violet.

Light due to waves of one simple frequency would produce the simplest color sensation, but homogeneous or monochromatic light is not possible to obtain because all color waves are compound. For instance, when sodium is burning, it emits a yellow light, yet that light is the compound of two yellows of separate frequencies but so close together as to become almost monochromatic. However, the human eye can receive compound waves of vibrations so close as to

form a single recognized color, the separate waves impinging so close together on the same spot on the retina as to blend the rays and thus give rise to that single color. The retina can perceive all waves from the red end of the spectrum to the opposite (violet) end. Colored lights are admixtures of several monochromatic colors, which the retina so blends as to give rise to a single sensation.

White light in general depends on the simultaneous compounding of all visible wave frequencies. In addition, it is possible to obtain whiteness by admixtures of certain separate colors, such as ultramarine blue and yellow, red and greenish blue, greenish yellow and violet; orange and greenish blue. Such colors are spoken of as complementary colors. It is a singular fact that when such pairs of solid pigments are mixed they do not produce white; for example, when blues and yellows are mixed, green is produced. However, when complementary colored lights are shown simultaneously to the eye, they always produce a white light.

Colors vary in hue, in purity and in luminosity—the hue names the color, the purity, by the absence of white light, the depth of the color, and the luminosity, or brightness, the shade or tone of the color. Thus, as white is mixed with a color, the color may become “brighter,” and if black is mixed, “dulness” follows—its luminosity fades. When a modified product is mixed with its pure complementary color, the result is not white but gray.

An analysis of the Young three component theory and the adaptation of von Helmholtz' pursuit of it, I accepted at the beginning as the groundwork of my studies.

It is of the greatest importance that the existence of color deficiencies be recognized.

There are many grades of “color blindness”—some persons are incapable of distinguishing the densest of red, or green, or blue, or even yellow. Others perceive these colors as through a hazy veil. Some persons may be defective in distinguishing only one, or at most two, colors, others, three or four. There are rare persons who see a colored picture only as though it were a black and white engraving, these persons have so-called monochromatic color vision. Accordingly, the various types of color blindness are usually described with regard to the number of colors definitely perceived and correctly named.

It has been interesting to note how persons with defective color vision adapt their perception to their needs, and few deal in colors. In their early years they learn what other people accept as the various colors, and, cautiously, they keep within those bounds. They seek to hide their defects. In childhood they have learned of their dissimilarity to their fellows, and they avoid necessity for color choosing. At the same time, their direct visual acuteness may be of the highest degree and range.

Of 230 boys in the upper classes of their school, 11 were found to have defective color sense, 1, the victim of hypophysial disease, had monochromatic vision. I endeavored to impress on the boys with defective color vision that they should not aspire to occupations, professions or positions requiring accurate perception of colors. In particular, they should not hope to become "fliers."

Color-blind persons seldom refer to their defects, rarely are they "vivacious." I have noticed how dull their mien is. By analogy, they remind me of trained singers whose tones lack something, they cannot keep exactly "on the key." I once knew a singer whose song selections were charming, but who avoided singing extemporaneously. He never joined in a hastily assembled quartet but offered, eagerly and readily, to sing the songs he had learned and prepared for.

Two patients with deficient color sense once took my attention. One was a capable chemist whose judgment of certain newly experimented-with compounds required exact estimation of their color. He was unable to match satisfactorily new compounds with the color of the standards. Another was a wallpaper designer. He was one of a family, largely of male members, with several generations of designers. The men of the family, therefore, were in close direct descent, but they had married into various families. The lad's skill in black and white was all that his father and grandfather demanded, but when delicate neutral colors were used he failed so sadly that he could no longer carry on the family tradition.

Every now and then there has come to me a young medical man desirous of entering ophthalmologic practice who has found it impossible to harmonize his description of the ocular fundus with the colors described by his chief. The eyegrounds resembled those obtained with red-free lights. These men remembered their difficulties in distinguishing the various stains in their earlier histologic courses.

I have known a few persons with unilateral color deficiency. It may be that persons with this condition are more numerous than has been reported. It is possible, also, that more precise investigation might yield interesting information concerning the whole subject of color vision. In the examination of railway men, I have tested each eye separately, both as a matter of precaution and with the possibility in mind of the presence of unilateral color blindness. A person with unilateral defect in color vision is unsafe, for if while in traffic he were to have one eye out of commission the defect might then become manifest.

The spectrum has been a useful instrument, with its six colors—red, orange, yellow, green, blue and violet. Indigo is sometimes included. To the normal persons all colors are distinct, from the red end to the violet end, but to others the red end, or the violet end, is cut off, so that

one appears black In my experience, the red end had been most often affected Two types of defective subjects have commonly been found—one perceives a full length spectrum, but with dull ends, the other perceives a spectrum with shortened ends These types have been found among persons who long have been classified as having red-green blindness Later, as now, their defect came to be spoken of as “protanopia,” for red blindness, and as “deutanopia,” for green blindness All sorts of deficiencies have been defined, from blindness in which only blue and yellow are perceived to a simple diminished sense of redness, in which the red, when vividly illuminated, may fully be perceived Such a sense is then spoken of as anomalous A person with anomalous trichromasy requires red and green to be concentrated, and he should be advised against seeking employment in occupations likely to become dangerous to life and safety—in conditions of mist, fog and smoke, or even agitation—as his responses might lead to disastrous consequences I regarded the results obtained in examination of the recruited Army nurses as indicative of “anomalous trichromasy” One set of skeins they spoke of as being “dull,” which may have been true, for the skeins were not as clean as were the skeins on my Thomson stick

Subjects with anomalous trichromasy are really in the “dangerous” class and should be studied with the greatest care They have aroused all my efforts, yet it has not always been easy to discuss their deficiency with them But by carrying out a variety of tests, and by more or less fatiguing the suspected subject, catching him at his lowest ebb, one can impress him with a knowledge of his weakness A normal person cannot become fatigued by such tests

In my early experience, I was impressed with the subject’s insistence on picking up the wools or the colored plates to examine them, as though he were myopic, even smelling them, and then laying them down cautiously, as though they were fragile and easily broken Defective art students have presented characteristics peculiarly their own They learn the appropriate colors to use for objects, such as green for trees and foliage and blue for skies, so that their product might readily be passed by the teacher I have often wondered whether “impressionists” may not have had defective color vision A noted artist, whose black and white or sepia studies had been awarded the highest honors at the Academy, aspired to be a portrait painter. Without his box of labeled colors, he was set to prepare an oil landscape The picture he presented, though perfect in outline and design, was colored beyond description, at which his fellow students derided him He was directed to pursue only “black and white drawing,” in which he was successful, becoming a distinguished book illustrator Though he is now dead, his works are still given high praise I

learned that his father was well known for his pen and ink drawings and for his etchings, but no oil paintings have been ascribed to him

The results obtained with "shadow tests" are hardly reliable, as they are really nothing but shadows, much might obstruct their being viewed and thus interfere with their clearness. To the subject with normal sight they can be of interest, for instance, if the specific color can be blocked out, the complementary color may appear followed by the after-image, to be named by the examinee. The color-blind subject easily becomes confused, as all sorts of variations result, blues and yellows appearing as green, red-green as red or gray and green-red as red or gray.

In my private practice I have employed the simple Thomson stick as a swift trial test. The speed and accuracy with which the examinee responds have served as an index of what to expect during a more prolonged examination. The Williams lamp, with its one to three roundels of various diameters, is employed with railway men. The men's confidence can thus be gained, and they are disposed to acquiesce in further questioning. The Edridge-Green lamp, in which the intensity of the reflections can be varied, is employed if there is hesitation or only deficiency. To the color-blind subject, a change in illumination produces a change of color. The simple Thomson lamp, with two disks, one of standard lights and one superimposed to modify the standards, has then been used. Despite the simplicity of this lamp, many a man has failed, the results being admitted and confirmed by his fellows who came to witness the testing in his behalf.

Then I use the so-called Japanese (Ishihara) pseudoisochromatic plates, which display numerals or splotched backgrounds, and the Stilling charts, which contain a greater number of plates than the Japanese. Certain of the Ishihara plates show an arrangement of the splotches which to normal subjects are not numerals, but the subject with defective color vision promptly gives them a number, or an outline is traced making a different figure than that presented. The first three or four plates are sufficient to judge the normal subject and others who view the spectrum. From the replies made to the remaining plates, one can be told whether or not they are expressing deficiencies in red-green vision. The Rabkin polychromatic tables are similar, displaying squares, cubes and triangles together with numerals, these have been, of distinct service to the Russians but are not now obtainable.

In recent years there has been much used a series published by the American Optical Company, based on the Ishihara plates. This series contains a greater number of plates than any of the Ishihara editions. Many active young men committed these plates to memory and glibly rattled off their replies. Persons who offer to cure color blindness depend on their teaching the testee to memorize the plates. The

numerals are of a more pronounced shade than are the backgrounds, so that they exhibit a distinctness which fades when the background is of the same shade, the numeral is then no longer visible. Munsell's "Book of Colors" has been much employed. It consists of many plates adopted by the National Bureau of Standards to serve as the standard of the hue of all the colors used in the arts and industries. Edridge-Green devised a set of plates splotted and lettered somewhat like the Ishihara and Stilling plates.

As a final test, I supply the wool skeins. By this time the man is exhausted, and it is then that his mistakes appear. Thomson's original stick held forty tagged and numbered skeins, the true skeins bearing the even numbers, 2 to 40 and the "confusing" skeins the odd numbers, 1 to 39. The sequence of the numbered skeins might have been learned, but it was sad to see an examinee endeavor to carry on his selections when the skeins were mixed on the stick, so that the groups corresponding to the rose section, the green numbers and the red numbers were arranged in a disorderly fashion, when the man's confusion became instantly manifest. The Jennings test is occasionally employed, this consists of true and confusing skeins, affixed to a card, beside each is a hole in the card, and under the card is a printed sheet, which is punched by a pointer, thus registering the true or false selection, the sheet thus serving as a record. In cases in dispute the Nagel anomaloscope or the simpler Chibert chromatophoroptometer may be used.

Color blindness, according to accepted descriptions, has been divided in three classes, or varieties. The first, or red-green blindness, is of the greatest importance, as signals on the highways, on the railways, in the air and at sea are red and green. The second class is that of persons who find it difficult to distinguish blue and yellow but who can perceive red and green. These colors are not of so great importance, except in some industrial and artistic employments. The third class is monochromasy, this type may occasionally be complained of by female subjects. Red-green type of blindness is found in male subjects, who have inherited it from male forebears, both directly and by transmission through the female members of a defective family. It may skip a generation and reappear in sons, conspicuously so, if the affected female carrier has married into a defective, but presumably unaffected, family.

Persons with red-green blindness commonly distinguish only the blues and yellows—they are classed as "dichromatic." Not all persons are affected with respect to the same colors, and to equal degrees. Their appreciation of the spectrum is various, and the bands are differently described; thus, they may be able to count all the bands but be decidedly uncertain about them.



While present day reports give a greater percentage of cases, I do not believe that color blindness is increasing, rather, investigation with improved methods has detected persons who in ordinary affairs have given no indication of their defect. According to earlier estimates, the percentage of affected males was 3 to 4, yet it has been found by several observers to be 9 per cent, and by another, 11 per cent!

"The color blind" is a somewhat unkind term applied to persons who are unable to distinguish certain colors correctly. It was introduced by Brewster about 1830, but it is not so cruel as the term "daltonism," after Dalton, the English chemist, who suffered from the defect. More recently, it is spoken of as "achromatopsia."

Despite the growing interest in the examination of persons who are believed to be normal, no new facts have been discovered in recent years which will aid in the solving of the problem of color vision. The theories are as fiercely contended by their advocates as ever. The various test methods have served to estimate the number of cases for each class of the responses. The history of color blindness is fascinating. Some day one may learn that the sense becomes manifest through the action of light on the chemical constituents of the retina.

317 South Fifteenth Street (2)

## IRIDOTASIS AB EXTERNO FOR RELIEF OF GLAUCOMA SIMPLEX

WILLIAM A STOUTENBOROUGH, M D  
COLUMBUS, OHIO

**T**HE PURPOSE of any operation for glaucoma is the reduction of intraocular tension, and to accomplish this at least one of three results must be accomplished (1) The normal intraocular pathway of drainage must be restored, (2) a new intraocular pathway opened or (3) a pathway formed for extraocular drainage. Many types of operations have been devised to accomplish these objectives. Of the first class, that is, operations devised to restore the normal pathway, iridectomy with its various modifications is the chief example. Cyclo-dialysis was thought by Heine, its originator, to accomplish the second objective the opening of a new intraocular pathway, and, while experimental work on rabbit eyes which I did several years ago failed to confirm his claim, gonioscopic examinations have demonstrated an opening in the iris angle in successful cases, indicating a fistula of the suprachoroidal space. The operations which have been done to produce pathways of extraocular drainage are the most numerous. Many have died a natural death. The chief survivors are Elliot's sclerocorneal trephination, Herbert's sclerectomy, LaGrange's iridosclerectomy, Holth's iridencleisis and Borthen's iridotasis. Of these, Elliot's trephination has undoubtedly been the most popular but in the last few years iridencleisis has grown in favor.

Until three or four years ago I practically always performed the sclerocorneal trephination for simple glaucoma. This operation was not always satisfactory, however, as in some cases the filtering bleb would flatten down and become adherent or the trephine opening would close over with scar tissue and the tension would rise again. In some cases the bleb would become too large. I also had a few cases of quiet iritis or cyclitis. Another danger is in getting the flap too thin. I, therefore, gave a great deal of thought to devising some method of eliminating these difficulties. It had been my practice to perform iridectomies for acute glaucoma through a scleral incision after reflecting a conjunctival flap. I believed that if I could combine some type of

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Read at a meeting of the Columbus Ophthalmological and Otolaryngological Society, Oct 7, 1946

filtering operation with the iridectomy in order to maintain a permanent filtration channel, this procedure would meet the requirements for relief of tension in chronic simple glaucoma. To accomplish this result, I have been doing a partial iridectomy through a scleral incision and inserting a tongue of iris tissue into the angle of the wound. Similar operations have, of course, been done before, but my experience with the operation described here has been so satisfactory that I should like to describe it again.

I have performed the operation in approximately 100 cases in the past two or three years, with almost universal satisfaction. In 3 or 4 cases of hemorrhagic glaucoma the results were not satisfactory and it became necessary to enucleate the eye.

Of course, the cases should be selected, as the operation is contraindicated when the iris is inflamed or the iris is atrophic. Synechias are likely to prevent a satisfactory incarceration of the iris. The operation may be performed either with general or with local anesthesia. I prefer "pentothal sodium" anesthesia, and if the patient is not arteriosclerotic, I usually give a retrobulbar injection of procaine hydrochloride-epinephrine hydrochloride solution to lower the intraocular tension.

If the operation is done with use of a local anesthetic, a subconjunctival injection of procaine hydrochloride-epinephrine solution or 2 per cent cocaine is given above the limbus. A conjunctival flap is then dissected down to the limbus, much as though a sclerocorneal trephine were to be done. The flap is held forward, and a scleral incision *ab externo* is made with a Tooke knife or a small scalpel, beginning 2 to 2.5 mm posterior to and paralleling the limbus. The knife should be so directed that the globe is entered about 1.5 mm posterior to the limbus. This brings one down on the root of the iris, a fact which is extremely important. As a rule, the iris begins to prolapse as soon as the anterior chamber is entered. The incision is carefully and slowly enlarged until it is 6 or 7 mm in length. The prolapsed iris is then grasped and withdrawn sufficiently to permit a meridional incision with scissors, which should include the pupillary margin. This incision is made at one extremity of the incision, and the surgeon, without releasing the grasp of the iris, tears the latter across. The tongue of iris tissue is then incarcerated in or wedged into the opposite end of the wound. If desired, an iris repositor may be used to secure the tongue of tissue in place more firmly. The iris pillar at the site of the meridional incision is replaced by massaging the edge of the wound externally by means of a repositor. The flap is then replaced and a running silk suture inserted to hold it in place. Blood is prevented as much as possible from entering the anterior chamber by using epinephrine and by holding the tip of a sponge over the incision. It is not always possible to prevent some blood from entering the anterior chamber, while this is undesirable, I have never seen any complications from it, as the blood has always been absorbed in a few days.

Occasionally peripheral adhesions of the iris or the synechias at the pupillary margins prevent prolapse of the iris, in which case a spatula may be used to break the adhesions or the flap may be pulled forward and the iris forceps inserted into the anterior chamber to grasp the iris.

Some surgeons caution against the use of atropine in iris inclusion operations for fear of pulling the tongue of iris out of the scleral wound. In my opinion, this fear is unwarranted, and I routinely instil atropine for a few days, until the postoperative reaction has subsided. Later, if the tension is a little slow in returning to normal, as occasionally happens, I may instil pilocarpine and employ gentle massage of the globe.

In my opinion, the advantages of this procedure over sclerocorneal trephination are as follows: 1 It is less difficult to carry out. 2 Each step is under perfect control, as a consequence, there is less danger of encountering difficulties, such as too thin a flap, buttonholing of the corneal flap or incomplete removal of the trephine button. 3 By performing the iridectomy through a scleral incision, the difficulty encountered with a shallow anterior chamber and the danger of injury to the lens experienced with use of instruments are obviated. 4 The eye is left in a safer condition and in less danger of secondary or late infection, such as sometimes occurs after trephination. 5 And of great importance, the root of the iris at the site of the iridectomy is removed, thus reopening the iris angle so that no iris tissue is left to push forward against the cornea and close the angle again. 6 By incarceration of the tongue of iris tissue in the scleral wound a permanent filtration channel is formed. It will be noted that, by 5 and 6, two of the three objectives in operating for glaucoma are accomplished in the one procedure.

As to the disadvantages, some persons may object to the keyhole pupil, but if its use results in reduction of tension and maintenance of sight, I do not consider it a disadvantage. Others feel that incarceration of iris tissue in a wound is poor and dangerous surgical technique; there is a great difference, however, between deliberate incarceration of a tongue of iris, including the pupillary margins, with which method there is no pulling or tugging on the iris and the tissue is constantly bathed in aqueous, and the accidental incarceration of iris tissue in a wound, in which case the tissue is usually in the form of a diverticulum from the posterior chamber without filtration and with a resulting cystoid scar, which remains irritable and is irritating to the contiguous ciliary body.

As I have said, my results with the procedure described have been almost uniformly satisfactory.

21 East State Street (15)

# A TANGENT SCREEN ILLUMINATOR

Construction, Use and Advantages

CONRAD BERENS, M D  
NEW YORK

AND

MATTHEW LUCKIESH, D Sc  
CLEVELAND

THE LUCKIESH-BERENS tangent screen illuminator previously demonstrated<sup>1</sup> was developed to provide for the lighting requirements necessary in the study of central visual fields with white and colored test objects. The illumination formerly proposed<sup>2</sup> was found to be lacking in some essentials for scientific work and for the comfort of the examiner. The general specifications established for the unit were as follows:

1 The illuminator should provide continuously variable illumination of from 1 to 100 foot candles

2 It should contain a means for quickly checking and adjusting the level of illumination

3 The level of illumination in the 25 degree zone of a tangent screen located 75 cm in front of the illuminator should not vary more than 10 per cent

4 The quality of the light should approximate that of daylight in order to minimize distortion of color

5 The color or spectral character of the light must not change as the level of illumination is varied

6 The entire unit should be simple to operate and should require a minimum of maintenance

7 There should be no necessity for tedious calibration of the device as the lamps deteriorate or when they must be replaced

8 Generated heat should be reduced to a minimum

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Construction was aided by grants from the John and Mary R. Markle Foundation, the General Electric Company, the Ophthalmological Foundation, Inc., the Department of Research of the New York Eye and Ear Infirmary, and the Department of Ophthalmology, New York University School of Medicine

1 Berens, C., and Luckiesh, M. The Luckiesh-Berens Tangent Screen Illuminator, read at the meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 15, 1946

2 Berens, C., Kern, D., and Payne, B. F. A Tangent Screen with Artificial Daylight Illumination, *Am J Ophth* 17:826-833, 1934

## CONSTRUCTION

The final design of the illuminator is shown in figures 1 and 2, which are front and rear views, respectively. The instrument consists essentially of a hollow square with fluorescent lamps mounted in white channels. These are covered with a system of adjustable sliding

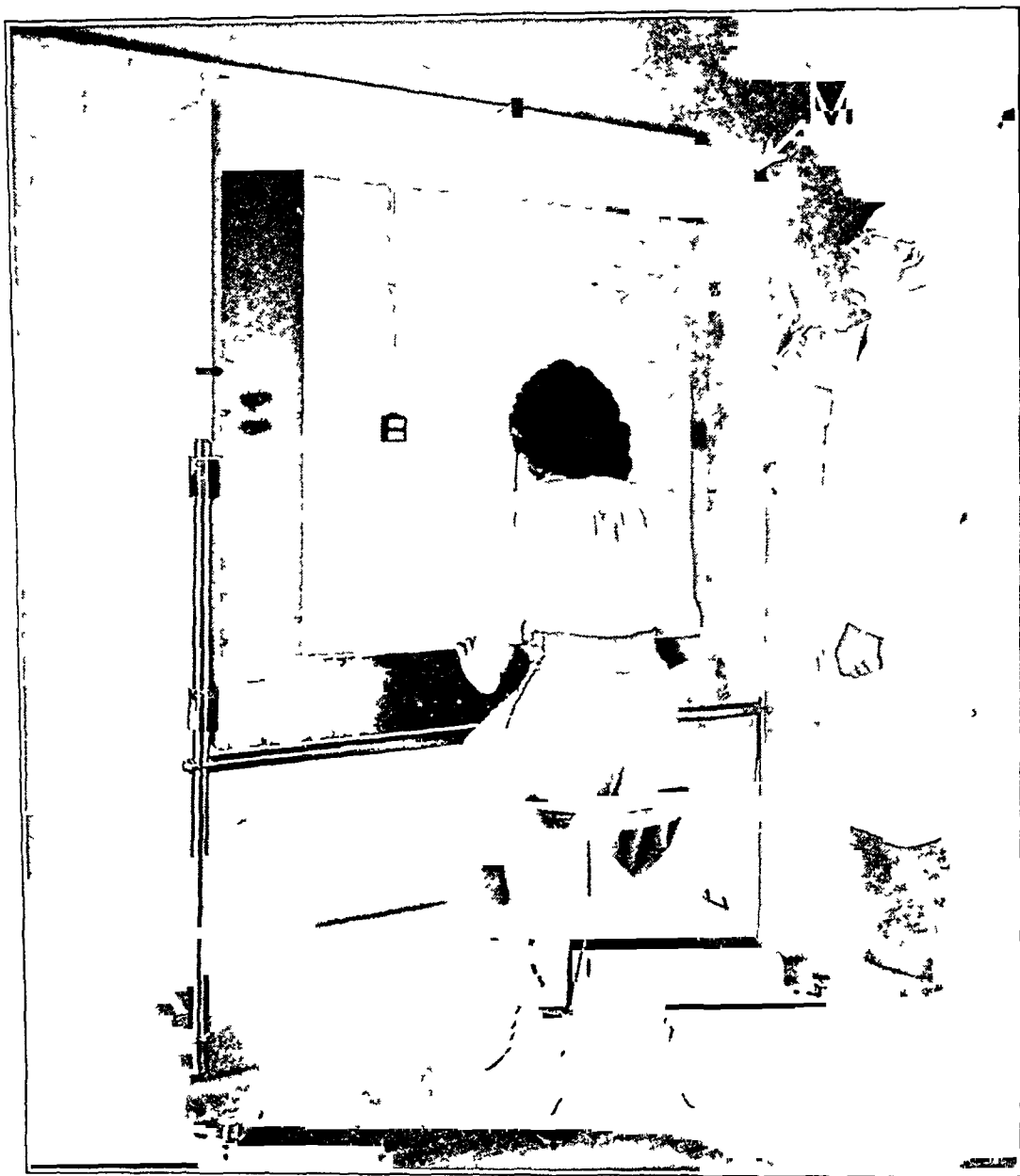


Fig 1—Front view of the tangent screen illuminator. The photocell is in position for measuring the foot candles on the tangent screen, and the operator is shown adjusting the illumination. The illuminated meter, *M*, can be seen in the upper right corner. The switches which control the fluorescent lamps are on the right hand base, convenient to the operator.

louvers for varying the illumination. The lamp channels forming the illuminating unit are 6 inches (15 cm) wide and 2 inches (5 cm) deep. Two 36 inch (90 cm) fluorescent lamps are placed side by

side in the channels on each of the four sides of the hollow square. This provides a total of eight lamps in the unit. The lamps are so connected that all are used for the higher levels of illumination, but only four are used for the lower levels. Two switches, an "on-off" and a "high-low," placed on the base of the right hand standard, control

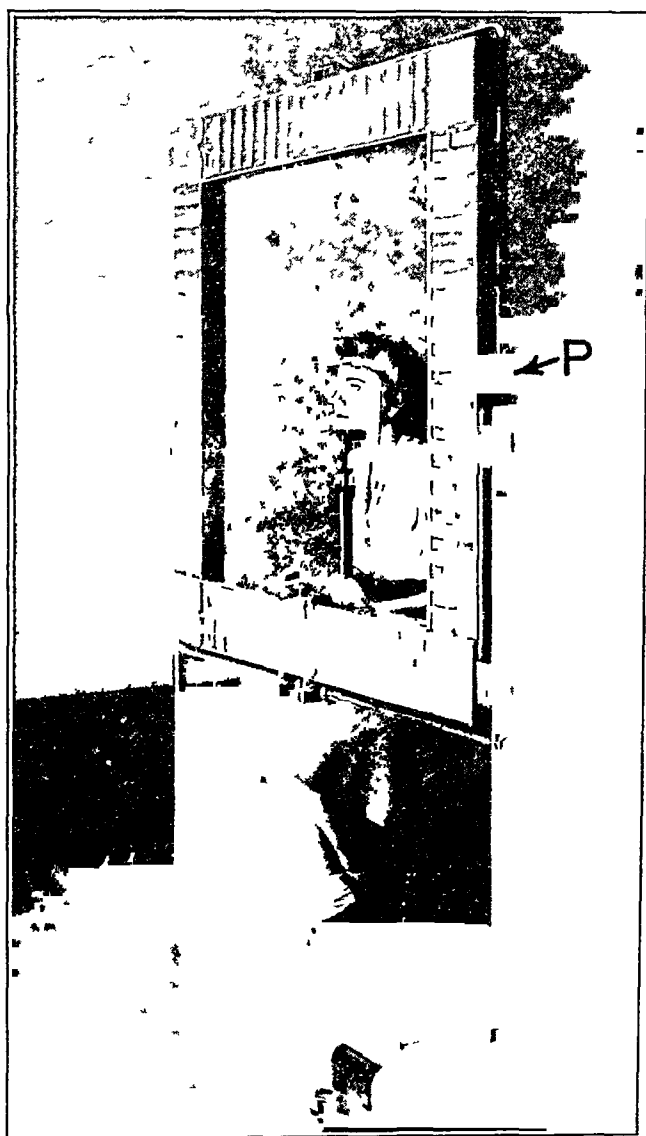


Fig 2—Rear view of the tangent screen illuminator, showing the louvers nearly fully open. The photocell, *P*, is in its retracted position at the right of the illustration.

the number of lamps being used. The level of illumination on the screen may be varied in infinitely small gradations from approximately  $\frac{1}{2}$  to 100 foot candles.

Thirty watt, 4,500 degree white fluorescent lamps are used. These provide an excellent color quality of illumination for viewing colored

test objects used in the determination of visual fields. Considerably less lamp wattage is required with fluorescent lamps than with filament lamps. This is an important factor in reducing the generated heat. The total wattage consumed by the unit, including the losses in the ballasts, is only 280 watts, as compared with over 2,000 watts if filament lamps were used.



Fig 3—Close-up view of the mechanism at each of the four corners for controlling the position of the louvers. All are operated simultaneously with the knob shown at the upper left corner.

A photocell, mounted on an arm, may be rotated outward and the cell placed in the center of the screen for measuring the illumination. In figure 1 the photocell is shown in the position for adjusting the illumination of the screen to the desired intensity, measured in foot candles.



In figure 2 the photocell, *P*, is shown at the left in the retracted position when not in use. The illumination is read on an illuminated meter, *M*, shown in figure 1 in the upper right corner of the unit. Two scales, measuring 0 to 10 foot candles and 0 to 100 foot candles, respectively, are available and may be selected by a switch directly below the meter. Thus all controls are readily accessible to the operator at the right hand side of the unit.

A knob at the upper right corner of the illuminator (fig 1) controls the position of the louvers. Figure 3 illustrates the control mechanism and the louvers, as well as the position of the lamps in the channel. The quadrant, *Q*, is rotated by means of a worm and gear mechanism. An accurately designed system of links slide the top and middle louvers, *A* and *B*, respectively, over the bottom, or fixed, louver, *C*. Identical quadrants and links are used in the four corners of the illuminating unit. The worm and gear control permits accurate adjustment of the level of illumination. The use of a series of three louvers, instead of two, permits greater light output, and yet the mechanism is relatively simple. The size of openings in the louvers is dependent on the movement from the fully open to the fully closed position. With two louvers, the open area would be less than 50 per cent of the total area because of the necessity of overlapping in the closed position. With three louvers, the open area is approximately 65 per cent with a corresponding increase in available illumination.

Fluorescent lamps have a long, useful life. On the rare occasions when it is necessary to change the lamps, they are reached from the rear of the unit. When the back plates are removed, the backs of the four hinged lamp panels are exposed. The release of two rotary catches permits each panel to be swung outward, bringing the lamps into position for easy cleaning or replacement. In figure 4, two of the back plates have been removed, and one of the lamp panels is swung outward. The fluorescent lamp starters may be changed without removing the back plates. They are exposed (fig 1) in pairs on each of the four slides of the hollow square.

The illuminating unit, with its center 48 inches (120 cm) from the floor, is supported on two heavy vertical rods, each rod mounted on a heavy plate. The entire device is 6 feet high (180 cm) and 4½ feet (135 cm) wide. Two large adjusting screws for leveling the instrument are incorporated in each base. Two two-lamp fluorescent ballasts are mounted in each of the two bases and each is covered with a housing.

An adjustable forehead and chin rest is mounted, as shown in figures 2 and 4. A sliding adjustment provides for varying the distance from the eyes to the screen.

The illuminating unit and the base covers are finished in a taupe-colored baked enamel, which is similar in appearance to a hammered finish. The louvers are of aluminum. All other surfaces, except the support rod of the chin rest, which is black lacquer, are chrome plated.

The distribution of illumination on the tangent screen is approximately the same for all levels of illumination from 1 to 100 foot candles.

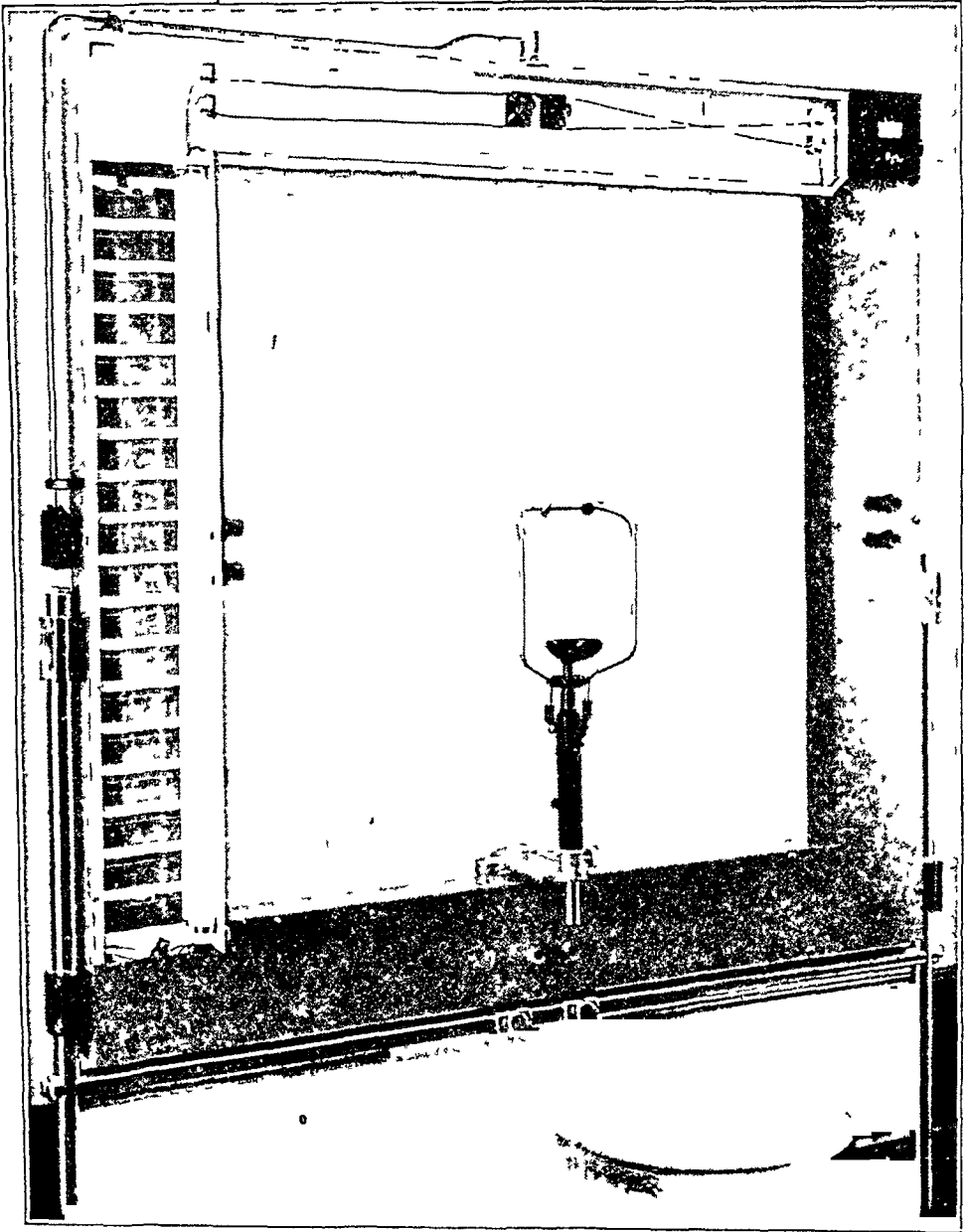


Fig 4—View showing two back plates removed and one hinged lamp panel swung out to illustrate accessibility of the fluorescent lamp. The slide adjustment of the head rest mount also can be seen.

With an illumination of 100 foot candles in the center of the screen, the illumination varies from 100 to 102 foot candles in the 25 degree zone and from 102 to 90 foot candles in the 35 degree zone. Thus, in the important central area, the illumination is essentially uniform.

## SUMMARY AND CONCLUSION

A tangent screen illuminator has been developed which because of the increased illumination available (100 foot candles) may be adapted to the examination of central visual fields with any tangent screen or surface. The illuminator was constructed especially for use with a neutral gray screen.<sup>1</sup> It permits charting from the front surface and the use of spherical colored test objects.<sup>4</sup>

The illuminator has been found to have the following advantages

1 It provides variable illumination of from 1 to 100 foot candles, which may be rapidly checked and adjusted without changing the color or the spectral character of the light

2 The illumination is quite uniform over a screen 2 meters in diameter, and there is only a 10 per cent variation in the central 25 degree zone

3 The quality of the light approximates daylight sufficiently for accurate testing with colored test objects

4 The apparatus is simple to operate and to maintain, and tedious calibration is minimized because of the built-in light meter

5 The low intensity of heat generated makes the patient and the examiner more comfortable

This tangent screen illuminator was designed and built in the Lighting Research Laboratory of the General Electric Company at Nela Park, Cleveland, where A. A. Eastman and S. K. Guth contributed much toward this satisfactory solution of the many problems involved

Nela Park, General Electric Company (12)

301 Fourteenth Street (3)

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3 Footnote deleted on proof

4 Berens, C., Evans, J. N., and Kern, D. White and Colored Spherical Test Objects for Use in Campimetry and Perimetry, *Tr. Sect. Ophth., A. M. A.*, 1931, pp. 407-409

# AMBLYOPIA EX ANOPSIA

## A New Concept of Its Mechanism and Treatment

B M LAZICH, M D \*

LOS ANGELES

THE PURPOSE of this paper is to present a new concept of the mechanism of amblyopia ex anopsia. It is hoped that the old theories will be reviewed and their present credence evaluated. Medical dictionaries and standard ophthalmologic texts perpetuate the definition of amblyopia ex anopsia as that amblyopia resulting from disuse of an otherwise normal eye. This point would be of academic importance only were not treatment of this condition involved which brings about improved results. This treatment hinges on acceptance of a new concept.

The following definition is offered as being closer to the actual conditions and therefore more tenable. Amblyopia ex anopsia is poor vision resulting from deviation of the visual axis from the fovea centralis to a point elsewhere on the retina where vision is less acute. It may be said that the greater the distance from the fovea, the less the visual acuity of this amblyopic eye as tested by ordinary means.

Before the analysis and the basis for the argument are presented, it may be stated that this discussion is centered about the experience in about 200 cases of amblyopia ex anopsia in private office practice during the several years following 1934. While granting that the number of cases may not be as great as desired, and that this experimental material does not lend itself to laboratory refinement, I feel certain, nevertheless, that the conclusions drawn are quite valid. All mention of amblyopia in this paper is limited strictly to amblyopia ex anopsia.

### PRESENT THEORIES REGARDING AMBLYOPIA EX ANOPSIA

1 Because of constant suppression of vision in the affected eye, the retinal elements become nonfunctioning, much as muscle fiber degenerates from disuse. Without questioning further the pathologic process which should take place if this were true, one may place this theory in doubt by observing that actually there is no cessation of stimulation to the retinal elements. Light may reach them easily at all times (unless occluded by opacities), and it is to light that these

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elements respond. Again, there are many cases in which good acuity is restored 'almost immediately to eyes which have been occluded for prolonged periods. I refer to cases of high refractive errors and to cases of cataract, which have existed for many years in some instances. Surely, if prolonged disuse were a factor, amblyopia should result, a complication which usually does not occur. The theory of amblyopia resulting from disuse is not plausible.

2 Because of constant suppression of vision, the cortical centers adopt a habit of "not seeing." The retinal elements and pathways are thought to be intact, but the visual impressions received on the retina are not perceived, or, rather, are suppressed by cortical processes.

This may explain certain aspects of suppression or suspension of vision, but not amblyopia. Suppression phenomena are complete and are not subject to the gradations of acuity on the Snellen chart, such as are found with amblyopia.

#### FACTORS COMMONLY ASSOCIATED WITH AMBLYOPIA

In analyzing my series of cases I tried to find those factors which appeared to have a bearing on the production of amblyopia. The following characteristics appeared with such frequency as to deserve mention.

1 Amblyopia was almost always monocular.

2 The refractive error was primarily hypermetropia, beyond the normal incidence of occurrence of hypermetropia. The hypermetropia was often of considerable amount, again beyond the incidence of occurrence of high hypermetropia. Only 2 cases of amblyopia with myopia were found.

3 When hypermetropia was found, it was almost always greater in amount in the amblyopic eye than in the good eye. This difference ranged from +0.25 to +4.00 D. It can be seen, then, that anisometropia occurred with unusual frequency.

4 Strabismus occurred in over 40 per cent of cases. The strabismus was chiefly convergent.

5 Finally, and most significant, the amblyopic eye was unable to fixate the object regarded, either monocularly or binocularly. The estimated true visual axis invariably failed to coincide with the object the patient was sure he was regarding.

#### PERTINENT PHYSIOLOGIC COMMENTS

Anatomically, the macular region differs from the rest of the retina in possessing a vast preponderance of cones. As the center of the macula is approached, the rods drop out completely and only cones are present. In the center of the macula is the fovea centralis, or central

pit, in which the cones are most closely packed, being thus the area of highest acuity, for visual acuity depends on the compactness of the retinal elements. As the fovea is left, visual acuity becomes progressively lessened as separation of the elements increases. Aubert and Foerster,<sup>1</sup> Dor<sup>2</sup> (1873) and Wertheim<sup>3</sup> (1894) investigated the relative acuity at various distances from the fovea in ordinary intensities of illumination. Wertheim derived a curve illustrating the variations in acuity from the fovea to the peripheral areas. This curve is not reproduced here, but an adaptation, in tabular form, of the findings from Aubert and Foerster is included.

Distance from Fovea	Angle of view	Acuity on the Snellen Chart
0 (fovea)	1	20 / 20
2° 32'	5	20 / 100
3° 15'	6	20 / 120
3° 51'	7	20 / 140
4° 17'	8	20 / 160
7° 14'	12	20 / 240
8° 32'	16	20 / 320
10° 15'	19	20 / 380
14° 57'	24	20 / 480
16° 17'	45	20 / 900
30° 20'	100	20 / 2000

It may be concluded from the data presented in this tabulation that at the center of the fovea visual acuity is at least 20/20 in the normal eye, and that as the distance from the fovea increases the acuity diminishes rapidly.

#### EVIDENCE IN SUPPORT OF NEW CONCEPT

It has been stated that the amblyopic eye does not use its true visual axis but, instead, uses a new visual axis, which falls outside the fovea. In so doing, the farther from the fovea the new axis falls, the less acute the vision.

The evidence is as follows.

1. At a convenient distance (1 meter), the patient fixes with the amblyopic eye (the other eye is occluded) an ophthalmoscope bulb. It will be apparent, on examination, that the corneal reflection of this bulb is eccentrically placed for such regard.

2. A second ophthalmoscope bulb of equal intensity, and at the same distance from the eye, is then aligned so that its reflection on the cornea is so placed that it should coincide with the true visual axis. It will be found that the second bulb lies on the same spatial arc a certain distance of arc away from the first, the distance roughly depending on the degree of amblyopia.

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1 Aubert, H., and Foerster. Untersuchungen über den Raumsinn der Retina, Arch f Ophth 3 (pt 2).1-37, 1857

2 Dor, H. Beiträge zur Electrotherapie der Augenkrankheiten, Arch f Ophth 19 (pt 3).316-352, 1873

3 Wertheim, T. Ueber die indirekte Sehscharfe, Ztschr. f Physiol u Physiol. d Sinnesorg 7.172-187, 1894

3 While he is fixing the first light bulb, the patient will be amazed to find, when questioned, that the second light (the one in the approximated true visual axis) is brighter and more easily seen. This is further evidence that the first visual axis in the preceding test is a false visual axis and is extrafoveal.

4 Now, while he is still fixing the first light bulb, the patient is asked to place his finger on it, to his surprise, he will find that as he fumbles for the first bulb his finger will unwittingly come much closer to the second. Apparently, the eye-hand coordination learned earlier in life has not changed and is still in sympathy with the true visual axis.

5 Mapping of a visual field will reveal that the plotted blindspot in the amblyopic eye does not correspond in position to that of a normal eye, but is displaced in a direction which coincides with the displacement of the visual axis, as predicted by the previous tests. (The visual field of an amblyopic eye is extremely difficult to take. The fixation of that eye is by no means as firm and steady as that of a normal eye, and the plotting, therefore, is rough and irregular. It is best accomplished by use of a stereocampimeter.)

6 Because the fixation of the amblyopic eye is uncertain and wavering, the visual acuity is not always the same but will easily vary a line on the Snellen chart, not only from day to day but even in the same examination. It is not at all uncommon for the patient to pick up an isolated letter here and there on Snellen lines much smaller than the one he is straining to read. With high degrees of amblyopia it will often happen that the patient says he can see the *E* when he looks at the door or other object alongside the chart.

7 By placing prisms of estimated values necessary to make the false and the true axis coincide, the examiner may often bring about momentary increased acuity. This effect is only transient, as the eye adjusts to the new condition and reassumes its false axis.

8 The final proof lies in the clinical results. If the treatment is directed to correcting the malprojection, progressive, rapid improvement takes place in a matter of weeks, instead of months or years. This is in sharp contrast to the simple occlusion treatment, which is based on the assumption that by forcing use of the amblyopic eye one will obtain return of vision.

9 As treatment is undertaken and vision improves, the aforescribed processes are reversed, and it will be found that when normal vision is reached a normal visual axis relationship is also reached.

#### PROCEDURE IN TREATMENT

Simply stated, the general outline of treatment which is carried out consists in correcting the malprojection and once again restoring the true visual axis relationship of object to fovea. One is aided tremendously in this endeavor by a strong eye-hand coordination habit, learned very early in life. It is necessary to awaken the patient to consciousness of his malprojection and then, by use of corrective treatment which includes this habit of eye-hand coordination, allow him to restore or recapture proper visual alinement. Ideally, after he has obtained correct alinement, it is desirable to assure him of maintaining the correction. It is attempted, therefore, to give the patient, in addition to good vision, a pattern of binocularism by fusion and stereopsis. Unfortu-

nately, in actual practice this ideal is not easily obtainable. In many cases the patient after obtaining substantial visual improvement feels that he has accomplished his temporary goal and wishes to terminate treatment. For all this, there is still a large number of patients for whom binocular vision and stereopsis have not been obtainable in spite of arduous efforts on the part of the patient. The only recourse is to maintain the visual gain by constant treatment at home, supplemented with periodic rechecks at the office. At present, no other alternative is in sight.

It is to be understood that, as in all branches of medicine, treatment is to a certain extent individualized. The problem of keeping up interest, especially in younger children, requires patience and considerable ingenuity. It is painstaking work, requiring a great deal of personal supervision, even though a well trained office nurse can give invaluable assistance.

From the beginning of treatment the problem of malprojection of the visual axis is brought home to the patient, who must have an insight into his situation. We make him conscious of his malprojection by the very tests used in determination of his amblyopia. He cannot fail to be impressed as his puzzling ophthalmic condition is revealed to him, and he will often begin to read a line or two better almost immediately.

It is desired to have the patient appear at the office for treatments of one hour each day, or, failing this, two or three times a week as a minimum. Exercises to be performed at home are designed to produce correction of malprojection, in much the same manner as in the office. This is accomplished by exercises for eye-hand coordination such as tracing letters and pictures, various games of skill—darts, indoor horseshoe pitching, chess, checkers, chinese checkers—in fact, a multitude of devices in which the eye is used with the hand and interest intensity is high. The patient, given the idea of what is desired, will invent and suggest other interesting and helpful projects. He does all these tests monocularly, of course, and always with the realization of, and desire to correct, his malprojection.

In the office, vision is checked before and after each treatment. Home exercises are discussed, and difficulties are ironed out. A large white board on which are pasted vivid red disks of various sizes, from  $\frac{1}{4}$  to 4 inches (0.6 to 10 cm) in diameter, is presented to the patient as the initial exercise. With this he is given a box of thumb tacks, which he places one by one into the center of each disk while his unaffected eye is occluded. Malprojection becomes obvious. The tacks are invariably outside the disk, and always in the same position relative to the disk. Afterward, he is allowed to see his work, and then he tries again. We allow him to use both hands, and even to feel his way into the disk. He is relearning eye-hand coordination.



If the patient uses a flashing light instead of constant illumination while doing his exercises, it is found that the improvement is much more rapid. It appears that each time the light flashes off, and then on again, a new adjustment in projection must be made by the eye, thereby increasing the total number of stimulations. Such intermittent light can easily be arranged by plugging in an interceptor, which cuts the light off and on every few seconds.

From pinning the tacks on the board, the patient then advances into the copying of letters, which are printed on another board. He is given a pencil with which he points out each individual letter, one at a time, as he copies. The flashing light method is used here, too. The important feature in this exercise is not so much the copying of the letters as the adjustment in projection as the subject points with his sharp pencil before writing down the letter. Early it is observed that, while pointing at one letter he will, unwittingly, read the adjacent letter instead. He progresses to smaller and smaller letters. This is a valuable exercise, which at the same time requires the minimum of supervision.

As a rule, by the time acuity of 20/70 is obtained, exercises are begun for development of fusion. For a few minutes after each monocular treatment the patient is shown simple cards requiring simultaneous macular perception with the stereoscope, the rotoscope or any other instrument available, for it is not the instrument but the variety one uses in order to maintain interest. From then on, increasing time is spent on fusion and stereopsis, at the same time, visual acuity is being developed.

#### RESULTS

In summarizing the clinical results of the treatment of about 200 patients in this series, I shall divide them roughly into three groups according to the visual acuity recorded on initiation of treatment. These groups represent approximately equal numbers of patients, but it must not be inferred that amblyopia ex anopsia occurs in this ratio in the general population.

The first group presented initial vision of 20/200 or worse, amounting at times merely to appreciation of hand movements. Of this group, 60 per cent achieved vision of 20/50 or better, and about 5 per cent vision of 20/20. Of the second group, which presented 20/70 to 20/200 vision on admission, ultimately 85 per cent acquired vision of 20/30 or better, and 15 per cent achieved 20/20 vision. The third group, which presented initial vision of 20/60 or better, concluded their treatment with 70 per cent showing 20/20 vision.

Of all patients treated, about 30 per cent agreed to take further treatment for development of stereopsis. Of those who agreed, less than one half obtained the desired end result.

The average duration of treatment was approximately six weeks, with an average of three and one-half treatments per week

Although age is a factor in success of treatment, it may safely be said that almost any age group can be treated successfully. In my particular series, the youngest patient was 4 years old and the oldest 41. In the same series, 52 per cent were between the ages of 5 and 15 years, 34 per cent were in the 16 to 25 year group, and 14 per cent were 26 years old or more. The majority of the adults treated were patients who sought improvement in vision in order to secure employment or pass an ophthalmic test for some other purpose. It was these patients in particular who wished to discontinue treatment as soon as their personal goal was reached. It was these patients, also, who were most anxious to secure some form of assurance as to their ultimate result in visual acuity.

#### ILLUSTRATIVE CASES

CASE 1—This case is not unusual except for the patient's age. It illustrates that disuse is not a factor in production of amblyopia, that age is not an impossible handicap in overcoming amblyopia and that simple treatment with occlusion is not very successful.

Mrs. A. T., aged 41, was first seen on May 3, 1938, complaining of poor vision in her right eye, which had been present all her life. As a child, occlusion treatment of the good eye for a year failed to improve her vision. Examination revealed low hypermetropic astigmatism in her right eye, correction of which did not improve vision beyond a doubtful 20/400. No improvement was apparent with the pinhole test. Vision in the left eye was 20/20, uncorrected. The best estimation of muscle balance revealed 18 D of exophoria in the right eye with 4 to 6  $\Delta$  base up, the blindspot of this eye as plotted on the stereocampimeter was enlarged and displaced slightly downward and considerably nasalward. The patient decided to take office treatments three times a week. The first treatment consisted in education regarding her malprojection. She was also instructed to place tacks into large red spots painted on a white board. At the end of the second treatment she had improved greatly at this exercise, and vision was 20/300. The third treatment consisted in the same treatment, with use of smaller red spots. She also began work with large letters under a flashing light. At the end of this treatment she read the 20/100 acuity line. At the end of the fourth treatment (or one and one-half weeks later), after she had worked on the chart under the flashing light, vision was 20/60. Fusion exercises were initiated, but she had no simultaneous macular perception. At the time of her ninth treatment she had second degree fusion and vision was 20/25—3. The blindspot had receded to almost its normal position. At this time circumstances prevented her continuing treatment.

In the main, this procedure is followed in all cases except as new ideas of minor importance are put into practice along the way. The following case reports are abbreviated for simplicity.

CASE 2—This case is also cited because of the patient's age.

J. W., aged 4 years, was first seen at the age of 2½ years, when she presented a left convergent strabismus of ten days' duration. A correction for compound hypermetropic astigmatism was prescribed. Two years later, on May 9, 1938, the convergent strabismus was not evident except when no correction was worn.

The refractive error had not changed appreciably, but since the child knew her alphabet surprisingly well a good check on visual acuity was possible. Vision was 20/25 in the right eye and 20/70 in the left eye, with correction. She was given five treatments for amblyopia, after which vision in the left eye became 20/30. Fusion exercises were introduced. As far as could be determined, stereopsis was obtained, but she had no further improvement in acuity.

CASE 3—This case illustrates rapid improvement in a patient whose original vision was extremely poor.

D K, aged 10 years, presented vision of 20/20 in the right eye. With the left eye only hand movements at 3 feet (90 cm) could be detected. On her first visit, on Dec 4, 1937, she was hardly able to place tacks in a circle 3 inches (7.5 cm) in diameter at a distance of 6 inches (15 cm). Vision after the first exercise was 5/400. At the end of the fifth office visit it was 20/300. Visits, however, became very irregular, but at the end of the tenth treatment, on Feb 12, 1938, she had 20/50 vision, at which time she was unable to continue.

CASE 4—This case is an unusual instance of amblyopia with myopia.

M B, aged 30, was seen on Jan 29, 1940. Visual acuity in the right eye was 20/400, corrected with  $-3.25$  D sph to 20/100. Vision in the left eye was 20/200 corrected with  $-1.50$  D sph  $\cap -50$  D cyl, axis 180 to 20/20. She made five office visits in February, after which vision in the left eye was 20/40. Five more treatments in March failed to improve vision further, although she acquired fairly good fusion, with no stereopsis.

CASE 5—This case is of the type so frequently seen with hypermetropia, anisometropia and internal strabismus.

T N, aged  $7\frac{1}{2}$  years, presented the chief complaint of internal squint since the age of 1 year. Visual acuity in the right eye was 20/25, corrected with  $+2.75$  D sph  $\cap +1.00$  D cyl, axis 95 to 20/20. Visual acuity in the left eye was 20/400, correction with  $+4.00$  D sph  $\cap +2.50$  D cyl, axis 90 gave no improvement. The estimated internal strabismus was about 30 degrees. Cooperation on the whole was rather poor, but after fifteen treatments, scattered over a period of three months, vision improved to 20/60+ in the left eye. There was no appreciable change in the strabismus.

The cases cited are not our "best" ones, but, rather, were picked at random to illustrate certain unusual factors. They indicate, too, the difficulties encountered in obtaining perfect cooperation with respect to office visits. On the whole, however, patient attendance was fairly satisfactory. Of course, the patients who made frequent, regular office visits benefited most in the shortest time.

#### COMMENT

In by far the majority of cases the amblyopia occurred in one eye only, in apparent agreement with all that is said about the assumption of dominance of one eye. In the cases in which amblyopia is present in both eyes, it is so much greater in one that the better eye can easily be said to be dominant. There are a few cases in which the amblyopia is almost the same in the two eyes. It is never great (rarely, 20/70). The amblyopia has always been found to occur with alternating strabismus.

Of the cases studied, a hypermetropia of 2.00 D and over was present in over 60 per cent. Lesser degrees of hypermetropia were found in 24 per cent of the series. Predominantly hypermetropic astigmatism was present in 15 per cent, and myopia in 1 per cent. It is to be understood that an eye without astigmatism is rare, and that in classifying the cases according to the results of refraction, as previously indicated we have permitted ourselves considerable leeway, by assuming the larger component to be the chief refractive error. This, of course, is oversimplification, but it does not materially alter the general conclusions.

The hypermetropia not only was predominant, but was greater, with 3 or 4 exceptions, in the amblyopic eye. The difference varied from +0.25 D to as much as +4.00 D on occasion, but in the majority of cases was between +0.25 and +1.00 D. The measurements were based on retinoscopic and subjective findings without cycloplegia. Since it is difficult to obtain accurate subjective data when amblyopia is present, any doubt as to the statistical results was settled by retinoscopic comparison. On application of homatropine the anisometropia decreased. The nonamblyopic eye then approached in plus acceptance the amblyopic eye. It was also noted that often as treatments progressed and vision improved the amblyopic eye had a tendency to lose plus acceptance and approach that of the good eye. This was not invariable, but occurred with such frequency that only a temporary correction was placed on the amblyopic eye until treatments were completed.

I have no explanation for these phenomena. Seemingly, the ciliary muscle loses a certain amount of tone under conditions of amblyopia. This is not as unphysiologic as it may at first appear. The progressive increase in plus acceptance by our patients at successive examinations at intervals of two or three years strongly indicates that the factor involved is a general loss of muscular tone reflected in the ciliary group. Be that as it may, no explanation will be attempted at this time.

It is to be emphasized that anisometropia in itself does not produce amblyopia. If it did, amblyopia would be found with myopic, astigmatic and hyperopic anisometropia, and in a ratio which does not conform with the facts. As a corollary, even hyperopic anisometropia is found with much greater frequency than amblyopia.

Clinical strabismus, chiefly convergent, occurred in association with amblyopia in about 40 per cent of cases. This is a striking frequency. Nevertheless, it may be said, from what has already been brought out, that the amblyopic eye by my definition possesses a subclinical squint. Surely, the relation of amblyopia ex anopsia and strabismus must be close. It certainly is not that of cause and effect. Amblyopia is found without strabismus and strabismus without amblyopia, moreover, the degree of one has no apparent effect on the degree of the other.

I cannot resist indulging in a bit of armchair philosophy. To me, the close association of these two entities means that they are at least parts of the same syndrome. This syndrome, however, originates in cortical processes, or in failure of the same. Binocular vision is undesirable; the nondominant eye deviates from its true visual axis only enough to destroy its existence, amblyopia ex anopsia results. Or, the deviation becomes excessive and strabismus results, in which case amblyopia may or may not be present.

If one does not postulate a cortical mechanism, how else can one explain the failures of surgical correction of strabismus? How often is it found after surgical overcorrection (recession or advancement or both) that the squint returns in a matter of days or weeks to almost the original degree? How often does one find that after a second operation the squint again returns in a short time? The problem is obviously one not of mechanics, but of mental aberration, a concept which explains why orthoptics in association with surgery is often of great help.

#### SUMMARY AND CONCLUSIONS

A new concept of the mechanism of amblyopia ex anopsia is presented, namely (a) Amblyopia ex anopsia is poor vision due to malprojection of the affected eye so that the visual ray is directed eccentrically to the fovea. (b) The degree of amblyopia varies as does the deviation from the fovea.

In support of this concept is produced (a) evidence of the deviation of the amblyopic eye as demonstrated by corneal reflections, (b) evidence of greater acuity when the true visual axis is approximated, (c) evidence that eye-hand coordination favors the original visual axis, (d) evidence of displacement of the blindspot as plotted on the visual field, a displacement which corresponds to the deviation demonstrated by corneal reflections, (e) evidence that improvement in vision is much more rapid and more certain if treatment is directed to correction of the malprojection, and evidence that as vision is improved by treatment the process of malprojection is reversed.

The procedure of treatment is outlined, with specific emphasis on the value of eye-hand coordination and of training devices which use intermittent illumination to increase the number of stimulations per treatment time.

The results are given in a few unusual cases.

The problem is discussed together with considerations of the possible relation of amblyopia ex anopsia to squint and the cause of squint.

In the light of what has been presented, I believe that the present definition of amblyopia should be reevaluated. In this paper, I have offered for consideration a new concept of the mechanism of amblyopia ex anopsia which appears more tenable.

# CONGENITAL IMPATENCY OF THE NASOLACRIMAL DUCT

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FROM a perusal of the literature, it would seem that congenital impatency of the nasolacrimal duct is a much rarer anomaly than our experience has led us to believe. In order to arrive at figures regarding the incidence of this condition and to learn the best method of treating it, the present study was undertaken.

Relatively few papers have appeared in the literature dealing with congenital impatency of the nasolacrimal duct, and almost without exception the condition has been described under the title of "congenital dacryocystitis." This term is a misnomer, since the underlying condition is not an inflammation of the lacrimal sac but, rather, an impatency of the nasolacrimal duct, the dacryocystitis occurring as a result of stasis. Another poor term appearing in the literature is congenital dacryostenosis, which implies simply a narrowing of the duct. This term should not be used, since it is not stenosis but, rather, a complete blockage which occurs. The only three papers which we have been able to find in the American and English literature suggesting a nomenclature at all compatible with the pathologic changes involved are those of Weeks,<sup>1</sup> Jackson,<sup>2</sup> and Zentmayer.<sup>3</sup> To our mind, the term congenital impatency conveys a much more accurate picture of the true pathologic process, in addition, it includes all cases in which both stasis and dacryocystitis occur, as well as those in which simply stasis without infection may exist. We suggest, therefore, that in the future this condition be known as congenital impatency of the nasolacrimal duct with or without dacryocystitis.

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1 Weeks, J E. Congenital Occlusion of the Lachrymal Canal, J A M A 43 1760 (Dec 10) 1904

2 Jackson, E. Delayed Development of the Lacrimal-Nasal Duct, Ophth Rec 16 321 (July) 1907

3 Zentmayer, W. Inperforation of the Lachrymonasal Duct in the New-Born, and Its Clinical Manifestations, J A M A 51 188 (July 18) 1908

Vlacovich,<sup>4</sup> in 1871, reported on 18 autopsies on newborn infants, in 4 of which he observed impatency of the nasolacrimal duct at the nasal end. It remained for Peters,<sup>5</sup> in 1891, Rochon-Duvigneaud,<sup>6</sup> in 1899, and Gunn,<sup>7</sup> in 1900, to recognize this congenital anomaly as the cause of epiphora, dacryocystitis and mucocele formation in the newborn. In an excellent article, Zentmayer,<sup>8</sup> in 1908, gave impatency of the nasolacrimal duct where this structure enters the inferior meatus as the commonest cause of congenital dacryocystitis, in addition, he cited 5 other causes of blockage of this canal, i e., (1) delayed separation of the cells of the epithelial cord, (2) annular folds in the duct, such as those of Hasner, (3) faulty development of cartilages in this region, (4) pressure by the inferior turbinate bone, and (5) pressure on the bones of the face with forceps during delivery.

The only figures on the incidence of this condition which we have been able to find are those recorded by Stephenson,<sup>8</sup> who observed that 1.75 per cent of 1,538 children in the outpatient department of a children's hospital had a lacrimal obstruction present since birth, and by Kipp,<sup>9</sup> who maintained that 10 per cent of all cases of dacryocystitis occur in children under 1 year of age. In neither survey was any effort made to include those cases in which the condition cleared spontaneously.

For a proper understanding of congenital impatency of the nasolacrimal duct, a short discussion of the embryonic development is in order. The generally accepted concept is that the maxillary process in its development overlaps the paraxial region around the eye and thus leaves a fold of ectoderm buried between it and the lateral nasal process. This is the rudimentary nasolacrimal duct. At about the 35 mm stage canalization of this rod of epithelial cells begins, owing to a disintegration of the cells of the central core. The process of canalization first begins in the inferior canaliculus, then proceeds to the superior canaliculus, then to the lacrimal sac and finally to the

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4 Vlacovich, G. P. Osservazioni anatomiche sulle vie lagrimali comunicate all'Accademia di Scienze Lettere ed Arti in Padova nella seduta del 12 Marzo, 1871, cited by Schwalbe, G. *Anatomie des Auges, Jahresb u d Leistung d Ophth* **2** 63, 1871.

5 Peters, A. Ueber die sogen Thranensack-Blenorrhoe bei Neugeborenen, *Klin Monatsbl f Augenh* **39** 376, 1891.

6 Rochon-Duvigneaud, A. Dilatation des voies lacrymales chez le fœtus et le nouveau-né consecutive a l'imperforation de leur orifice inferieur. Conditions anatomiques qui favorisent la dacryocystite congenitale, *Arch d'opht* **19** 81, 1899.

7 Gunn, D. Lacrimal Obstruction in the Young, *Ophth Rev* **19** 31, 1900.

8 Stephenson, S. A Preliminary Communication on Affections of the Tear-Passages in Newly Born Children, *M Press & Circ* **119** 103, 1899.

9 Kipp, C. J. Dacryocystitis in Nursing Infants, *T Am Ophth Soc* **2** 537, 1879.

nasolacrimal duct itself The last portion to become patent is that of the puncta and the opening into the inferior meatus The average age at which the lacrimal system finally becomes patent throughout is the eighth intrauterine month, and failure of the duct to become patent by the time tear formation begins, shortly after birth, gives rise to epiphora, dacryocystitis and mucocele formation

The more recent, exhaustive studies of Fischer<sup>10</sup> on the formation of the nasolacrimal apparatus indicate that some of these concepts are in need of revision According to him, and he has excellent evidence to support his claim, the nasolacrimal groove, or sulcus, forms alongside the line of fusion between the maxillary and the lateral nasal process, and the anlage of the nasolacrimal apparatus then develops beside this groove as a thickening of epithelium, which sinks into the embryonic connective tissue of this region This ridgelike epithelial thickening then detaches itself from the surface epithelium and assumes a cordlike or rodlike form, broadened at the upper end From this point his views as regards canalization are in close agreement with those generally accepted

#### PRESENT STUDY

A series of 200 unselected, consecutive newborn infants at the Medical College of Virginia, Hospital Division, and St Luke's Hospital was studied The incidence of epiphora and dacryocystitis was noted, as well as the date on which symptoms of impatency disappeared The only treatment employed was the local application of a penicillin ointment containing 1,000 Oxford units per gram of ointment base three times a day and daily massage by the mother over the region of the sac

In 5 cases, not included in this series, in which probing had to be carried out, iodized oil USP was injected through the inferior punctum and roentgenograms were taken to learn at what level blockage had occurred In 3 of the cases the impatency was unilateral, and in 2 cases both sides were affected

In the series, 12 instances of congenital impatency, as manifested by epiphora and the presence of mucopus after pressure over the affected sac, were found In 10 cases the epiphora appeared between the tenth and the twelfth day after birth, while in 2 cases tearing was delayed three and four weeks, respectively Although mucopus could be expressed in every case, the employment of penicillin considerably reduced the amount of discharge, prevented conjunctival injection and completely eliminated incrustation of the lids Symptoms disappeared

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<sup>10</sup> Fischer, F Die Entwicklung der ableitenden Tränenwege beim Menschen, *Abhandlungen aus der Augenheilkunde und ihren Grenzgebieten*, no 22, Berlin S Karger, 1936



in every instance without its being necessary to resort to probing, the longest interval being five months, the shortest three weeks and the average 2 3 months. One case, in which the patient did not return for follow-up study, though included in the series, is omitted from the statistical survey. In all but 2 cases the left side alone was involved, while in 1 case involvement was bilateral and in another only the right side was affected. We are unable to offer any explanation for the heavy dominance of involvement of the left side. All the infants with congenital impatency were term babies. A statistical summary of the series is given in the table.

Since the study of the original series was concluded, 5 cases have been observed in which the condition failed to clear up after conservative measures had been employed for six months. In these instances

*Statistical Summary of Twelve Cases\* of Congenital Impatency of the  
Nasolacrimal Duct in Newborn Infants*

Case No	Sex	Age at Onset of Epiphoria	Duration of Symptoms	Side Involved	Discharge on Pressure on Sac
1	M	12 days	5 mo	Left	Gross
2	F	11 days	4 mo	Left	Gross
3	F	4 weeks	3 mo	Left	Gross
4	M	12 days	3 mo	Left	Gross
5	M	10 days	2½ mo	Left	Gross
6	M	11 days	2 mo	Left	Gross
7	F	12 days	5 weeks	Both	Gross
8	F	3 weeks	1 mo	Left	Gross
9	M	10 days	1 mo	Left	Gross
10	M	10 days	3 weeks	Left	Gross
11	M	11 days	3 weeks	Right	Gross
12	M		Not heard from	Left	Gross
Average (case 12 not included)		13 5 days	2 3 mo		

\* In all cases the impatency occurred in term babies. The incidence of congenital impatency in the entire series of 200 infants was 6 per cent.

we resorted to probing, and after such treatment the condition cleared immediately. This procedure was carried out, with the patient under ether anesthesia, after iodized oil had been injected through the inferior punctum and roentgenograms taken. In 2 cases involvement was bilateral, and in 3 cases only one side was affected. In every case the roentgenogram revealed a well filled sac, but no opaque material could be seen below in the duct. It might be concluded from this observation that in such cases the blockage is at the junction of the sac and the nasolacrimal duct, but we believe that, instead, the iodized oil has simply failed to enter the duct, which is either collapsed or filled with detritus. This belief is borne out by a simple experiment in hydraulics which we carried out.

A cellophane soda straw was cut the same length as that of the lacrimal sac and nasolacrimal duct and was occluded at each end. It was then filled to two-thirds capacity with colored water, and two small openings, 2 mm apart, were made into the upper third of the tube

Iodized oil was injected into the lower opening and the results were noted. Only the upper third filled, and the oil did not displace any of the water but regurgitated through the upper opening. From this experiment we have concluded that the presence of the oil in the sac only does not necessarily mean that the occlusion occurs at the level of junction of the sac and duct but, rather, indicates that the oil has failed to enter the duct.

In figure 1 the roentgenogram reveals well filled sacs in a case of bilateral impatency.

In all 5 cases probing was carried out with the No. 1 Bowman probe through the superior punctum and canaliculus, after the punctum

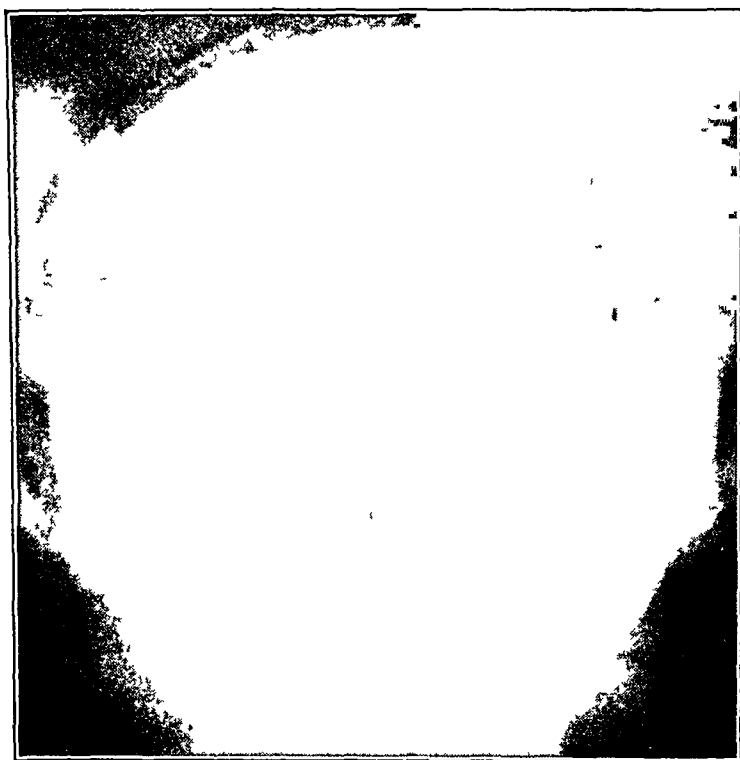


Fig. 1—Anteroposterior roentgenogram, showing sacs well filled with iodized poppyseed oil, but none below this level.

was first dilated with the punctum dilator. We have found this much the simpler procedure, since the probe forms an acute angle with the longitudinal axis of the nasolacrimal duct and passes readily into the sac and duct with but slight upward rotation of the probe. The ease of this procedure is in sharp contrast to the difficulties encountered when the probe is passed through the inferior punctum and canaliculus, a procedure which necessitates an upward rotation of the probe of well over 90 degrees, resulting frequently in the creation of a false passage. The procedure is illustrated in figure 2.

In every instance, probing was carried out with extreme gentleness, the probe being allowed to find its own way, without forcing. When

the probe has reached the nasal floor, this being readily ascertained by the length of probe which has passed into the sac and duct, a submucous elevator is passed beneath the inferior turbinate process until the probe is encountered. At this time a sharp metallic click can be heard and felt. On rare occasions in which the duct is abnormally long or is redundant, the probe may enter the inferior meatus and still remain covered with mucous membrane. If the probe is felt to be covered with a cushioning layer of membrane, as detected with the submucous elevator, it should be vigorously rubbed with this instrument until the bare metal is encountered. The probe may then usually be seen, particularly if the inferior turbinate process has been shrunk with cotton pledgets steeped in epinephrine solution. After the probing has been carried out and patency established, the No 1

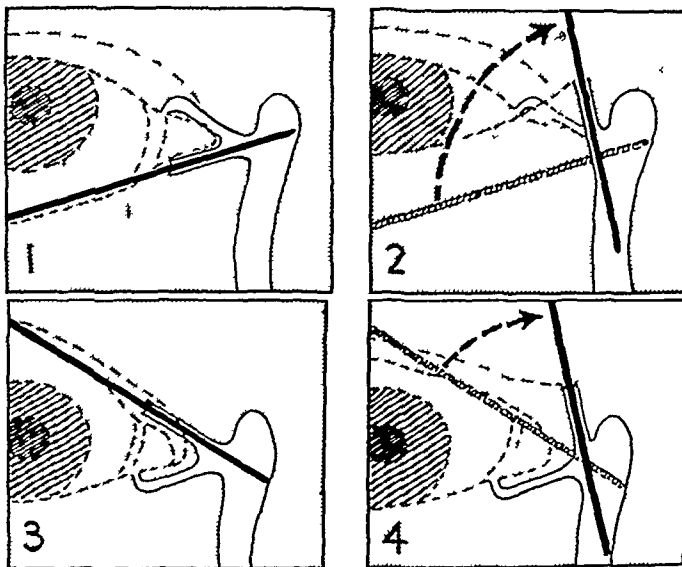


Fig 2—1 and 2, diagrammatic sketches, showing difficulty of probing through the inferior punctum and canaliculus, in contrast to 3 and 4, illustrating the ease of probing through the superior canaliculus. 5 and 6 are artist's drawings of actual probing through the superior punctum and canaliculus.

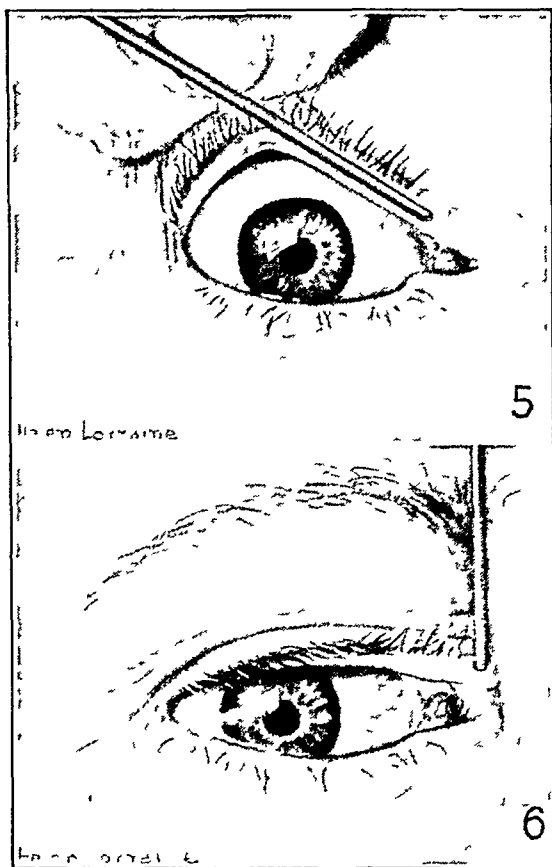
Bowman probe is passed through the inferior canaliculus in order to assure patency of that structure also. Figure 3 A and B show, respectively, posteroanterior and lateral roentgenographic views of the Bowman probe in place.

#### COMMENT

In a series of 200 consecutive, unselected newborn infants, 12, or 6 per cent, were found to have congenital impatency of the nasolacrimal duct. To ophthalmologists who see, for the most part, only cases in which the impatency has failed to clear up spontaneously, this figure will come as something of a surprise. Indeed, so high an incidence will no doubt surprise many pediatricians also who are unfamiliar

with the picture of congenital impatency of the nasolacrimal duct and who dismiss cases of this anomaly as being instances of "stubborn conjunctivitis" At any rate, the condition is one of much greater frequency than is generally realized, and one in the treatment of which close cooperation of pediatrician and ophthalmologist pays off in good dividends

In all our 12 cases cure was effected by the simple expedient of employing penicillin ointment and massaging the sac This therapy is in accord with the teachings of Weeks,<sup>1</sup> Wood,<sup>11</sup> Peters,<sup>5</sup> Jackson<sup>2</sup> and Riser,<sup>12</sup> who advised conservative treatment for several months



before resorting to probing, and is at variance with the beliefs expressed by Cutler,<sup>13</sup> Gifford<sup>14</sup> and Mayou,<sup>15</sup> who advised early probing From our observations, we are convinced that the more conservative measures

11 Wood, C A A System of Ophthalmic Operations, ed 1, Chicago Cleveland Press, 1911, vol 2, p 1592

12 Riser, R O Dacryostenosis in Children, Am J Ophth **18** 1116, 1935

13 Cutler, C W Cases of Delayed Opening of the Naso-Lachrymal Septum in the Newborn, with Consequent Dacryocystitis, Arch Ophth **32** 289 (May) 1903

14 Gifford, S R A Hand-Book of Ocular Therapeutics, ed 1, Philadelphia, Lea & Febiger, 1932, p 223

15 Mayou, M S Lachrymal Abscess in the New-Born, Roy London Ophth Hosp Rep **17** 246, 1908

followed by probing in the more recalcitrant cases (arbitrarily, those with duration of symptoms of over six months), offer the best method of treating this condition. This is particularly true now that one has the sulfonamide drugs and penicillin with which to control infection.

We are convinced that when probing must be carried out it should be done with the patient under general anesthesia, and not as an office procedure, as advocated by Goar<sup>16</sup>. Our reasons for this are threefold:

- 1 The infant can be kept absolutely still, so that gentle, unhurried probing can be carried out, thus greatly reducing the number of false passages made.
- 2 The annoyance of a crying infant, which distresses waiting parents, and other patients as well, is eliminated.
- 3 The inferior meatus can be explored and the probe located and freed from overlying membrane, if need be, a procedure which, as Berry,<sup>17</sup>

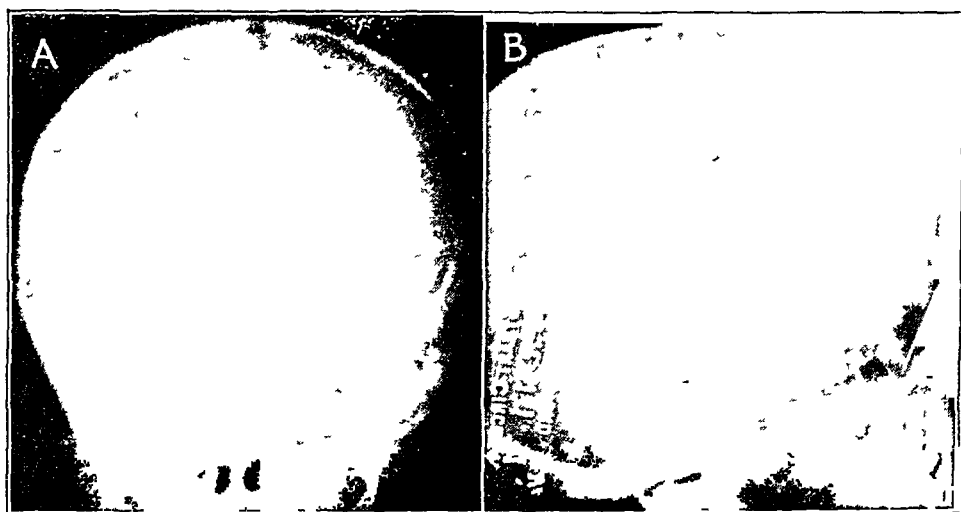


Fig 3—*A*, posteroanterior roentgenogram, showing the Bowman probe in place. The end extends into the inferior meatus.

*B*, lateral view, showing the Bowman probe in place. The angle at which probing must be carried out is well shown.

Woodruff,<sup>18</sup> Gunn<sup>7</sup> and, more recently, Larsson<sup>19</sup> have emphasized, is essential if success is to be assured.

In our hands, probing through the superior punctum has been found to be eminently satisfactory. When probing is carried out thus, the probe falls naturally into the sac and glides easily along the mesial wall into the duct. The ease of this maneuver is in contrast to the difficulties encountered when probing is carried out through the

16 Goar, E. L. Infantile Dacryostenosis, *M. Rec. & Ann.* **37** 611, 1942.

17 Berry, J. C. Treatment of Obstruction of the Lachrymal Duct, *Boston M. & S. J.* **160** 541, 1909.

18 Woodruff, H. W. Congenital Dacryocystitis, *Illinois M. J.* **60** 380, 1931.

19 Larsson, S. Treatment of Congenital Atresia of the Nasolacrimal Duct, *Acta ophth.* **16** 271, 1938.

inferior punctum, a procedure in which the entering probe runs head on into the mesial wall and, to enter the duct, must be rotated through a wide angle, a maneuver in which it is easy to force a false passage Gifford<sup>14</sup> advocated passage of the probe through the superior punctum and canaliculus, but he first split the canaliculus and then introduced a No 5 Bowman probe. We feel that this procedure is unduly traumatizing, and in our hands all that has been necessary is simple dilation of the punctum, followed by introduction of the smallest Bowman probe.

#### SUMMARY

The term "congenital impatency of the nasolacrimal duct," instead of the terms "congenital dacryocystitis" and "congenital dacryostenosis," should be used. In a series of 200 consecutive, unselected newborn infants, 12 cases of congenital impatency of the nasolacrimal duct were found, an incidence of 6 per cent. In all cases the condition cleared under conservative measures, consisting of daily massage of the lacrimal sac and local application of penicillin ointment. All the infants were term babies.

In cases, not included in the series, in which probing was resorted to (after six months of conservative treatment), the No 1 Bowman probe was introduced through the superior punctum and canaliculus after dilation of the punctum with the dilator, with the patient under ether anesthesia. The inferior meatus was explored with a submucous elevator and the probe located and rubbed until bare metal was felt. Cure was effected in all instances.

Injections of iodized oil U S P through the inferior punctum revealed well filled sacs but no radiopaque material in the duct, an observation which was due probably not to a blockage at this level but, rather, to failure of the material to enter the duct.

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#### ABSTRACT OF DISCUSSION

DR J V CASSADY, South Bend, Ind. The authors advise conservative treatment of dacryocystitis in infancy. They believe that the nasolacrimal duct should not be probed until every device has been used to clear up the infection by conservative treatment. I recently reviewed the literature and reported a series of cases in which I probed the duct early. I concluded that prolonged conservative treatment may be more harmful than prompt opening of the obstructed duct.

One should concur with their use of the term congenital impatency of the nasolacrimal duct, which indicates the etiologic factor in the dacryocystitis. As the authors point out, the condition is neither congenital dacryocystitis nor congenital dacryostenosis. In other words,

almost all dacryocystitis of infancy follows atresia of the duct because this structure has failed to open at birth

As they have pointed out, in a large number of newborn infants the nasolacrimal duct is not patent Schwartz (*Beitrag zur Versammlung deutsch ophth Gesellsch* 50 30-35, 1934, Congenital Atresia of the Nasolacrimal Canal ARCH OPHTH 13: 301 [Feb ] 1935) found the ostiums closed in 35 per cent of late fetuses, while Dr J Parsons Schaeffer, in a personal communication, said

This report that the ostiums of the nasolacrimal duct were closed in 35 per cent of fetuses during the last few months of pregnancy is, I believe, a conservative statement I have occasionally noted complete absence of the nasolacrimal membranes during the seventh and eighth fetal months, but it is much more typical to find such membranes present at and shortly after birth

Many lacrimonasal membranes rupture spontaneously at or soon after birth, before tears form and symptoms of dacryocystitis appear Dacryocystitis in newborn infants is rare during their stay in the hospital, in a survey of 1,000 newborn babies, only 1 case was found within the first week after birth

If dacryocystitis appears, it will not be cured until the obstructing membrane is ruptured In the authors' first cases, spontaneous resolution of the infection occurred after several months of conservative treatment, but in their later cases, in spite of six months of conservative treatment, patency did not occur until they probed the duct I have had prompt subsidence of symptoms in a large number of infants by sounding the duct early The probing was done as an office procedure, with local anesthesia, without injury to the lacrimal passages The authors believe that conservative measures, followed by probing in the more recalcitrant cases (arbitrarily those with duration of symptoms over six months), offer the best method of treating this condition Conservative treatment for one or two months should be sufficient to ascertain whether the atresia of the duct will clear up spontaneously Considering that cure can be effected so easily with a single sounding of the duct, I believe this measure should be carried out

The authors advocate using the upper punctum and canaliculus if it is necessary to probe the duct I have usually used the lower one, and in 100 cases I have seen no untoward effects or damage to the lacrimal passages I have used the upper punctum and canaliculus in only a few instances Their argument and the drawings illustrating it seem logical

DR JOHN H DUNNINGTON New York The authors have correctly termed this condition congenital impatency of the nasolacrimal duct, for, as they have pointed out, it is not a stenosis of the duct and the dacryocystitis is a sequela of the impatency Their finding of 12 cases of congenital impatency in a series of 200 consecutive newborn infants is both interesting and surprising This condition is more frequent than is generally realized, for the average ophthalmologist sees only cases in which spontaneous canalization does not occur I am in entire accord with the authors' desire to withhold instrumentation, and I believe, as they do, that in most cases the obstruction will respond

to expression. The percentage of cures by expression will increase greatly if one adheres to a technic described by Crigler (Crigler, Lewis Treatment of Congenital Dacryocystitis, J A M A 81:23 [July 7] 1923)

1 The tear sac is allowed to become fully distended. We caution the mother not to wipe the eye or in any way to press on the tear sac before coming to the clinic or office. She is given a 25 per cent solution of protargin mild (argyrol) or other antiseptic eye lotion, to be dropped into the culdesac three times a day, to protect the eyeball from infection.

2 The infant's head is held between the surgeon's knees in a manner similar to the method in vogue of inspecting the eyeball. Assuming that it is the right sac that is affected, he places his right thumb over the sac in a way to shut off the return flow through the puncta. This is done by holding the thumb sidewise, with the thumb nail outward and forming an acute angle with the plane of the iris. The edge of the thumb is now pressed downward over the puncta, compressing it against the rim of the orbit, with this point of pressure maintained, the thumb is rotated to the right, at the same time pressing downward, abruptly, over the sac. The fluid, now being compressed by the thumb, transmits the pressure to the walls of the sac, which must give way at its weakest point, which happens to be the site of the nasal opening.

If care is taken that the thumb is applied in such a way as to prevent regurgitation into the conjunctival sac and sudden pressure is exerted over the distended lacrimal sac, the retained fluid will frequently burst the persistent fetal membrane at the lower end of the nasal duct. Crigler reported that he had had no failures after seven years' use of this procedure. In my hands it has not been uniformly successful, but has produced a cure in so many instances that I can heartily recommend its trial.

There is general agreement that probing should be carried out when conservative measures fail, and I agree with Dr. Guerry and Dr. Kendig on the advisability of performing it with the patient under general anesthesia. Although I have always followed the conventional technic of entering the sac through the inferior punctum and canaliculus, I see no objection to the method described here, unless it be to the use of such a small probe. I believe in the maxim, "The smaller the probe the greater the chance of creating a false passage", so I uniformly introduce a no. 3 probe into the duct.

PROF. DR. RAUL ARGANARAZ, Buenos Aires, Argentine. I shall try to explain why massage and probing are successful in curing dacryocystitis in nearly all newborn children, and why the same treatment applied to adults with the same malady has failed in nearly 90 per cent of cases.

The cause lies in the anatomic and pathologic structures, which are entirely different in the newborn infant and in the adult. In the case of the newborn infant the closure of the inferior opening of the nasolacrimal duct results in wide dilatation of the entire sac and bony structure, while in the adult the growth of inflammatory fibrous tissue blocks the nasolacrimal duct for its entire length.



DR EVERETT L GOAR, Houston, Texas I agree with the authors that it is good therapy to treat this anomaly conservatively, but conservatism can be carried too far In any case in which the duration of impatency of the lacrimal duct goes beyond a few months a stricture is likely to form that is hard to relieve It is a simple matter to stretch the lower punctum with a sharp-pointed punctum dilator and to slip a no 1 or no 2 Bowman probe into the nose It is unnecessary to give the baby a general anesthesia The hardest part of this procedure is to hold the baby's head still between the knees, at the same time everting the lower lid to expose the punctum A well trained assistant is necessary Usually one probing is enough There is, therefore, no reason for wasting valuable time in applying hydrostatic pressure over a long period

DR DUPONT GUERRY III, Richmond, Va Dr Kendig, who is a pediatrician, will express the pediatrician's point of view

DR EDWIN L KENDIG JR, Richmond, Va As a pediatrician, I wish to stress three points First, congenital impatency of the nasolacrimal duct is of common occurrence, as shown in the figures Dr Guerry and I have presented, second, conservative treatment is effective in the vast majority of cases, and, third, six months seems to be an adequate period of trial of conservative therapy

Two of the discussers have expressed the belief that probing should be done early, but several pediatricians with whom we discussed the paper and the matter beforehand stated their opinion that conservative therapy should be given a trial even longer than six months, and no pediatrician consulted was willing to have probing done before the age of 6 months

## SPONTANEOUS ABSORPTION OF CONGENITAL CATARACT FOLLOWING MATERNAL RUBELLA

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NEW YORK

THE OCCURRENCE of cataract and other congenital defects in infants born to mothers who had rubella during the early part of the gestation period has become well known in the few years since 1942, when Gregg<sup>1</sup> first noted the connection in Australia and Reese<sup>2</sup> published the original American report two years later. Although various other ocular defects, especially microphthalmos, nystagmus and glaucoma, have been frequently noted, little attention has been paid to another, most interesting finding in a few of the eyes.

Some of these cataracts have been needled, but, surprisingly, only a thin membrane was found, dividing readily as a result of the instrumentation originally intended solely to open the anterior capsule and expose the lens fibers to the action of the aqueous.

Gamble<sup>3</sup> was the first to report such a membranous cataract. In 1945 he described the case of a baby girl who when first seen at the age of 6 months had in each eye a membrane with a dense central area and a less dense peripheral area, through which a faint red reflex could be seen. The lens of the right eye required needling three times, as the membranous cataract proved to be "rubbery" and moved with the knife, making it difficult to achieve an incision. The last operation on this eye was performed with use of two Ziegler knives at the same time, a procedure which proved to be more effective than the use of one knife only. The membrane of the left eye was successfully needled on the first attempt. In passing, it is noteworthy that this child was born in 1935, before the current decade, in which the connection between congenital anomalies and rubella during pregnancy was appreciated and which has provided all other recorded cases.

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From the service of Dr. Edward Bellamy Gresser at the Beth Israel Hospital.  
Read at a meeting of the New York Society for Clinical Ophthalmology,  
Feb. 3, 1947.

1 Gregg, N. M. Congenital Cataract Following German Measles in Mother, *Tr. Ophth. Soc. Australia* 3: 35, 1941.

2 Reese, A. B. Congenital Cataract and Other Anomalies Following German Measles in the Mother, *Am. J. Ophth.* 27: 483 (May) 1944.

3 Gamble, R. C. Membranous Cataract Due to Rubella in the Mother, *Am. J. Ophth.* 29: 737 (June) 1946.

Long and Danielson<sup>4</sup> presented a series of which case 3 was the first of the cases of membranous cataract to be published, although Gamble's case had been presented at a meeting a few months earlier. This case was that of a male infant, born at term, in whom bilateral cataracts were observed shortly after birth. The entire pupillary area of each eye was opaque. At the age of 6 weeks, a discission was performed on the right lens, but a clear pupil was not obtained. Seven months later, when a similar procedure was performed on the other eye, a vertical incision made through "a soft membranous" cataract resulted in the immediate appearance of a clear opening.

The third such case was described by Blake<sup>5</sup>. In 1944 he saw a 2 month old baby with small eyeballs, alternating esotropia and roving nystagmus. On dilation of the pupil, the lenses showed a white, asbestos-like opacity, with no clear cortex. The mother stated that she had had rubella during the second month of her pregnancy. Bilateral discissions were performed six months later. When the knife needle was drawn across the capsule, the membrane divided readily, leaving a clear, black pupil at once. No soft lens matter was present, and there was practically no reaction after the operations.

A similar case, in which, however, no history of rubella could be elicited, was presented by Jeancon<sup>6</sup>. When the discission was performed, only an empty capsule was found, which opened without any cortex being evident. There was practically no postoperative reaction. Eleven months later the left eye was operated on with a similar satisfactory result.

#### REPORT OF A CASE

B. S., a white girl, was born on Nov. 16, 1943, at Woman's Hospital, New York. The obstetrician (Dr. G. Gordon Bemis) stated that the delivery was a prophylactic one with low forceps, the birth was four weeks premature, and the infant weighed 4 pounds 2 ounces (1,870 Gm). Except for rubella during the first month, the pregnancy was entirely uncomplicated. Shortly after birth it was noted that the baby had what appeared to be congenital cataracts. When she was examined a few days later, dense white cataracts were seen, although incomplete pupillary dilation prevented study of the periphery of the lens. The pupils reacted to light. The eyes were of normal size, and the anterior chambers were shallow. The corneas were clear. The ocular tension seemed normal on palpation. No other congenital defects were found by the pediatrician.

At the next examination, on May 12, 1944, no change in the appearance of the cataracts was noted. Four months later the opacification of the right lens

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4 Long, J. C., and Danielson, R. W. Cataracts and Other Congenital Defects in Infants Following Rubella in the Mother, *Arch. Ophth.* **34**: 24 (July) 1945.

5 Blake, E. M. Congenital Membranous Cataract, *Am. J. Ophth.* **29**: 464 (April) 1946.

6 Jeancon, E. C. Congenital Cataracts in Children, *Am. J. Ophth.* **28**: 904 (Aug.) 1945.

was observed to be definitely less dense, and a red fundus reflex could be seen through the thinner portions of the membrane. After another three months the lens showed similar clearing and gave the impression of undergoing absorption. With the passage of time, the clearing process in the lenses slowly, but gradually, progressed. Alternating esotropia and nystagmus developed. The child had sufficient vision to walk about safely and to recognize large objects. She had been found to be deaf.

Despite the presence of some useful vision and the apparent continuation of the clearing process in the lenses, it was decided to perform dissections so as to provide the best possible sight to enable the child to attend a school for the deaf. Accordingly, in November 1946, Dr. Edward B. Gresser needled the right lens which promptly and easily divided, presenting a black pupil and no evidence of any lens substance. Because of the ease of the procedure, the left lens was operated on while the child was still under the anesthesia. This time the membrane did not divide, but tore loose from its attachments and rolled up to form a small ball in the anterior chamber. There was no reaction in either eye the next day. After one week the right eye showed the same satisfactory pupillary opening but the free membrane in the left had unrolled and attached itself to the anterior surface of the iris, covering the pupil. This eye has not yet had a second operation, which is now indicated. The parents report that the child shows obvious and pronounced improvement in vision since the operation.

#### COMMENT

There can be no doubt that definite lenses were present at birth in this infant and that these lenses subsequently were absorbed. The reports of the other cases previously mentioned were analyzed to learn whether such absorption also may have occurred.

Jeancon<sup>6</sup> stated that the parents of the infant she reported observed that the white masses in the pupillary areas were much more intensely white shortly after birth than at the first examination, a year later. At that time a fair red reflex could be seen, and three days later the right eye was operated on. When the child was seen again, after a year's interval, the capsular opacity appeared as dense as at the first examination, but there was a better red reflex, which led the author to conclude that further absorption of cortex had taken place.

Gamble<sup>7</sup> saw his patient first in March 1936, when she was 6 months old and he stated the belief that the lenses had more thickness at that time than later. The right lens had snowflake-like opacities, and the left lens was diffusely opaque; the peripheral areas were less opaque than the center. By 1939 the lenses appeared to be membranous with a dense central area. The first needling in 1940, on the right eye showed that the lens was semimembranous with some cortical material liberated by the operation. The first needling on the left eye, in 1943, showed the lens to be definitely membranous with no cortical material.

When the possibility of spontaneous absorption of the lens was considered in the previously described case from the series of Long and

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7 Personal communication to the author.

Danielson, Dr Long<sup>7</sup> wrote that the needling was performed on the right eye when the child was about 8 weeks old, at which time a definite lens seemed to be present, and not a membrane, although the inability to dilate the pupil widely may have made the examination misleading. That a thin membranous cataract was observed at operation on the left eye performed seven months later, Dr Long considered suggestive of some absorption of the lens substance with the passage of time.

The difference in the condition of the lens operated on second in each of the 3 cases just discussed supports the belief that there was at least some loss of lens substance in the interval following the first operation. In no case was there such a definite and observable change as took place in both eyes in the case reported here, but the process appears similar. The mechanism of the absorption of the lens material is open to speculation. Jeancon assumed that her patient had morgagnian cataracts in which complete absorption took place. Such an explanation does not apply to the present case, as no liquefaction was seen, but it is possible that there occurred small, even microscopic, areas of liquefaction from which absorption took place too rapidly after their formation to permit them to achieve grossly observable dimensions. Microscopic study by Swan<sup>8</sup> of the lenses of 3 infants who died of congenital defects following maternal rubella during pregnancy showed massive necrosis in the lenses of 2 with vacuolation. Absorption of the fluid from such vacuoles with constant development of new vacuoles, which were absorbed in turn, would result in a gradually thinning cataract and ultimate membranous transformation.

Duke-Elder<sup>9</sup> stated that congenital total cataract represents a general opacity of all the lens fibers, which, presumably, is the result of a severe disturbance acting throughout the entire period of development. In some cases the lens may shrink, forming a membranous cataract and producing the condition of pseudoaphakia. The shrinkage of the lens results in a deep anterior chamber and a tremulous iris, and the pupillary area is occupied by remnants of the capsule, which may show considerable epithelial proliferation. Duke-Elder did not make clear whether this formation of membranous cataract occurs after birth or prior to it, resulting in the latter event in a congenital membranous cataract. Admittedly, this is not especially important, as the moment of birth is an incident of no great developmental significance in the life cycle of the lens, in particular of this type of cataract.

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8 Swan, C. A Study of Three Infants Dying from Congenital Defects Following Maternal Rubella in the Early Stages of Pregnancy, *J Path & Bact* 56 289 (July) 1944

9 Duke-Elder, W. S. Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol 2, p 1373

Membranous cataract and its development from congenital cataract have been recognized for many years, but the subject apparently is unfamiliar to many ophthalmologists. All that Duke-Elder has to say on the matter has already been presented, and the comprehensive texts of Berens and Bellows make no mention of it whatever. The absorption of the lens material from cataracts in children was briefly mentioned by Fuchs<sup>10</sup>; but, interestingly, the best description of the condition that I have seen was published one hundred and thirty-eight years ago. The following quotation from Saunders'<sup>11</sup> treatise on diseases of the eye is of clinical, as well as historical, interest.

The efforts of nature in disease are seldom stationary, and even when they fail to accomplish the cure, the correctness of the intention may be clearly discerned: thus in the congenital cataract, after the crystalline lens is converted into an opaque substance, it is gradually absorbed, and in proportion to the progress of the absorption, the anterior lamella of the capsule retires upon the posterior until they form one membrane which is white opaque and very elastic. This is the conversion of the lenticular into the capsular cataract: all that is capable of being absorbed, nature herself removes, and she only fails to accomplish her purpose, because the capsule cannot be destroyed by this process.

This description applies obviously to the condition reported here, even to the ultimate necessity of performing dissections because of the partial obstruction to sight. The observation that the membrane is very elastic confirms the difficulty that Gamble had in dividing the membranous cataract in his case.

#### SUMMARY

A hitherto unreported development in congenital cataract following maternal rubella is its spontaneous absorption, leaving only a membrane in its wake. Such an absorption has rarely been seen in congenital cataracts of presumably other origins. A case in which the process occurred is described. Four other cases in which this process may have taken place, in three of which the mother had rubella during the early part of the pregnancy, are cited.

211 Central Park West (24)

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10 Fuchs, E. *Text-Book of Ophthalmology*, translated by A. Duane, ed. 7, Philadelphia, J. B. Lippincott Company, 1924, p. 635.

11 Saunders, J. C. *A Treatise on Some Practical Points Relating to the Disease of the Eye*, London, Longman [and others], 1811, p. 132.

# DISTANCE DISCRIMINATION

## I Theoretic Considerations

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THE EXPERIMENTAL technics and psychophysical methods utilized in the testing of binocular distance discrimination are not new developments, many features are to be found in standard texts. The present exposition is an attempt at a closer integration of certain elements of physiology with those of psychophysical methods, by which it is believed that greater significance may be obtained for both. A brief statement of the problem will first be made, and then those points significantly affected by the present outlook or procedure will be expanded.

The customary method of measuring distance discrimination is to present two objects, such as vertical rods, which may be made to differ in distance from the observer. These are seen through an aperture in a screen, thereby excluding certain cues. Nevertheless, the exclusion of cues other than retinal disparity or binocular parallax is by no means as complete as is often imagined, the size cue, for example, is seldom eliminated. For the present, however, only retinal disparity will be considered.

Retinal disparity is the difference between the retinal images, consequent on the lateral separation of the eyes. If great enough, these image differences are interpreted as differences of distance. The linear displacement of one test object with respect to the other may be converted to an angular difference of separation of the retinal images, and it is in this form that the threshold of distance discrimination is commonly presented<sup>1</sup>. As in all such cases, the threshold must rest on a statistical basis.

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<sup>1</sup> Duke-Elder, W S. Text-Book of Ophthalmology, St Louis, C V Mosby Company, 1940, vol 1, p 1077

When more than two rods are used they may be arranged so as to appear at the same distance as the object being fixated, the locus of such apparently equidistant points constitutes one form of the horopter. An analysis of the relations of the retinal images of objects so arranged furnishes the basis for the concepts of corresponding and noncorresponding areas—important elements in the theory of binocular vision.

The discrimination of distance may be tested in the manner previously described or by the stereoscope, which presents two pictures the retinal images of which differ in the same way as do the images of the test objects just discussed.

By one of several statistical methods, the judgments obtained in the test are made to yield a threshold. The physiologic and psychophysical principles involved deserve careful consideration, for two reasons: (a) A valid comparison of thresholds requires either that all conditions be the same or that these conditions be specified and that the effect of variations therein be known, (b) analysis shows that the threshold data contain information on two physiologic aspects of distance discrimination which have not hitherto been properly distinguished and evaluated.

With this outline in mind, further discussion will be devoted to an elaboration of points considered new or necessary to the total argument.

#### 1 GEOMETRIC AND STATISTICAL ASPECTS OF THRESHOLD OF DISTANCE DISCRIMINATION

The relationships involved in binocular parallax are diagrammed in figure 1. The eyes are looking at  $A$ , and  $M$  and  $N$  are the nodal points of the left and right eyes, respectively. The retinal images of  $A$  are  $a_l$  and  $a_r$ ; and since  $A$  is being fixated, these fall on the two foveas. A second object,  $B$ , may be moved along a line  $BN$ , parallel to  $AM$ , five positions are indicated by the subscripts 1 to 5.  $B$  will form an image on the temporal portion of the retina of the left eye and on the nasal portion of the retina of the right eye. Regardless of the position of  $B$ , its image on the right retina will be at  $b_r$ . On the left retina, however, depending on the position of  $B$ , its image will be at  $b_1, b_2, \dots, b_5$ .

When  $A$  is fixated, there will be a position of  $B$  which will be judged equidistant, this will be at or near  $B_1$ . The exceptions are important but will be considered later. At  $B_1$  the visual angle separating  $B_1$  from  $A$  will be the same in the two eyes ( $\angle b_rNa_r = \angle b_1Ma_l$ ), the images of  $B_1$ , lying at the same distance and in the same direction from the foveas, will be fused, and  $B_1$  will appear as a single object on the right of, and at the same distance as,  $A$ . When the second object is at some much greater distance, as at  $B_1$ , the angle  $b_1Ma_l$  is smaller than angle  $b_rNa_r$ , and when it is much nearer, as at  $B_5$ , the angle  $b_5Ma_l$  is greater than angle  $b_rNa_r$ , if these differences of angle are sufficient,



the observer will report seeing  $A$ , the object fixated, as single and  $B$  as double. Certain other positions,  $B_2$  and  $B_4$ , for example, which lie closer to  $B_3$  and give angles differing from  $b_1Na_r$ , but to a lesser degree than in the previous case, will lead to reports of  $B$  as single and farther or nearer than  $A$ . Slight differences will thus lead to fusion and the perception of a third dimension, greater differences will lead to diplopia, both may be considered as differing degrees of retinal disparity.

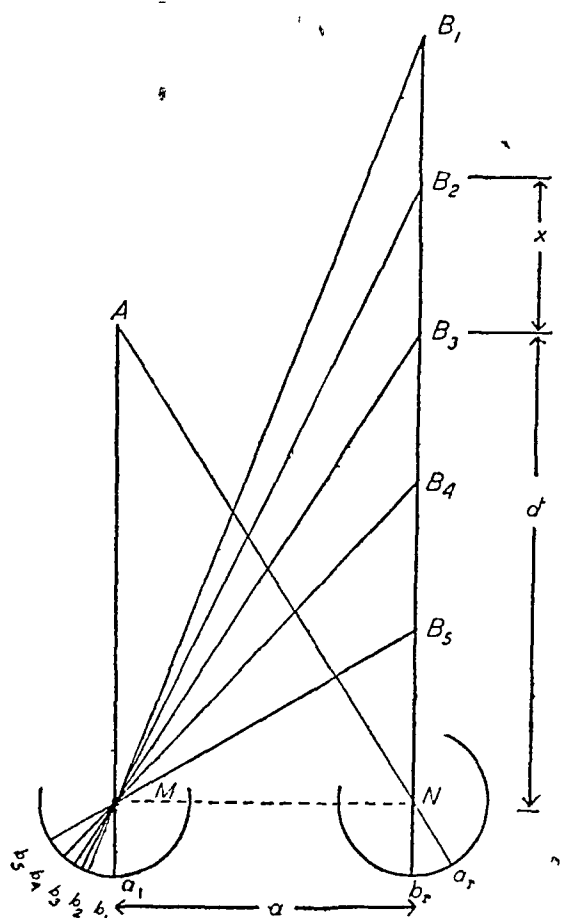


Fig 1—Relations involved in binocular parallax.

Certain other angular relations may now be mentioned. The parallactic angle of  $B$  with relation to the two eyes is angle  $NBM$  and that of object  $A$ ,  $NAM$ . Depending on the position of  $B$ , its parallactic angle will be smaller than, equal to or larger than that of  $A$ . The customary threshold of distance discrimination is the difference between the parallactic angles of  $A$  and  $B$  when  $B$  is judged to be just noticeably nearer or farther than  $A$ , this angle is commonly designated by the Greek letter eta ( $\eta$ ). It must be remembered that the diagram is not to scale: the interpupillary distance,  $NM$ , is approximately 6.5 cm, and

the distance of  $A$  and  $B$  from the eye, about one hundred times as great. The separation of the targets is about that of the eyes, but may be greater or less in the amounts actually employed in the present experimental work without invalidating the relations considered in the following discussion.

As diagrammed, the parallactic angle of  $A$ ,  $NAM$ , is equal to the visual angle separating  $A$  and  $B$  for the right eye,  $a_rNb_r$ , while the parallactic angle of  $B$ , or  $NBM$ , is equal to the visual angle separating  $A$  and any position of  $B$  as seen by the left eye,  $a_lMb$ . The formula for the difference in binocular parallax of two objects, or binocular disparity ( $\eta$ ), may be derived as follows. Assume  $a$  to be the interpupillary distance and  $d$  the distance from the nodal points to the fixed object  $A$ . If  $B$  is perceived to be "just noticeably far" at  $B_1$ , then the linear threshold is expressed by the equation

$$B_1 - B = x$$

The parallactic angle of  $A$  is  $NAM$ , and its tangent is  $\frac{a}{d}$ , the parallactic angle of  $B$  is  $NB_1M$ , and its tangent is  $\frac{a}{d+x}$ . Since the angles are very small (of the order of 1/100 radian), the tangents may be taken as the measure of the angles in radians. Since  $\eta$  is the difference between the two parallactic angles,

$$\eta = \angle NAM - \angle NB_1M = \frac{a}{d} - \frac{a}{d+x} = \frac{ax}{d^2 + dx}$$

and since  $d$  is very large as compared with  $x$ , the denominator may be considered as  $d^2$  without appreciable error. The formula thus becomes

$$\eta = \frac{ax}{d^2}$$

where  $a$  is the interpupillary distance,  $x$ , the linear threshold, and  $d$  the distance of the targets from the observer.

Because of the relations pointed out between the parallactic angles of the objects and the visual angles of the separation of the objects,  $\eta$  is a measure of the difference between the parallactic angles. Obviously, the smaller the linear threshold  $x$ , the smaller will be its transformation,  $\eta$ .

The distance  $x$  has so far been treated as a single fixed distance, but, as in the case of other thresholds, it (or its transformation,  $\eta$ ) is a statistical constant, a point that has often been lost sight of in calculating or comparing measures of binocular distance discrimination.

The linear threshold of distance discrimination has, like other thresholds been variously defined, it is clear that it must be either a rough approximation or a statistically obtained value. To emphasize the statistical nature, imagine, for example, that ten or one hundred reports are obtained for various positions of the movable rod along the line  $B_1-B$ . With the rod at position  $B$ , the reports would all be "single," and probably all "equidistant." As the rod receded toward  $B_1$ , although the reports would still be "single," those of "far" would

begin to appear, and the number of "equal" reports would decrease until with the rod at  $B_2$  all reports would be "single" and "far." As the rod continued toward  $B_1$ , the reports of "far" would continue and those of "double" would appear and increase until with the rod at  $B_1$  all reports would be "far" and "double."

The divisions into five categories ("double," "single," "near," "far" and "equal") would hardly be useful in any practical situation, but it is introduced to illustrate the importance of instructions to the observer and the possible perceptions that occur in distance discrimination. Thus, in one experiment in this laboratory the instructions for the setting of the movable rod were "equal," "just noticeably far" and "just noticeably near." The distributions about these points ( $B_1$ ,  $B_2$  and  $B_4$  of figure 1) were such that no overlapping took place, thus, there were positions which were too far to be called "equal" and not far enough to be called "far." These facts are not unknown in psychophysics but have often been overlooked in the study of distance discrimination, and for this reason they deserve reemphasis.

The case of two points may now be extended to a series, for example, the five points  $B$ ,  $C$ ,  $A$ ,  $D$  and  $E$ , of figure 2, lying in the horizontal plane which passes through the nodal points of the two eyes, the so-called horizontal horopter. The objects and the two nodal points are diagrammed as lying on the circumference of a circle, the angles  $MAN$ ,  $MBN$ , and so on will be recognized as equal because all intercept the same arc  $MN$ . This is the Vieth-Müller circle, or horopter. The diagram is geometrically correct but two difficulties are encountered in its practical application: one statistical and the other physiologic.

In the first place, the points are determined by certain statistical and subjective criteria. Aguilonius,<sup>2</sup> who introduced the concept, thought of the horopter as "the sum of all points seen single while the point of sight remains unchanged." Other subjective criteria will be considered presently. For any subjective criterion there may, however, be various statistical criteria, say, a 75 per cent threshold, so that there are, in fact, a series of possible horopters rather than a "horopter."

To turn to the sensory basis, the parallactic angles of the points on the Vieth-Müller circle are equal, and, the visual angles separating a particular point (such as  $E$ ) from the fixation point  $A$  are equal for the two eyes. Owing among other things, to optical differences consequent on differences in length and refractive power, the linear retinal separations are not always equal and the spatial values for equal retinal separations are not always equal. In consequence, the commonly stated requirement of identical physical relationships of corresponding points is not a correct generalization, although it may happen as an individual

<sup>2</sup> Aguilonius, F. *Opticorum libri sex*, Antverpiae, ex off. Plantiniana, 1613

peculiarity The following quotation from Best and Taylor<sup>3</sup> will illustrate the type of definition alluded to

For any fixation position of the eyes a line can be drawn by geometrical calculation along which any point is imaged on a corresponding point in each retina

The retinocortical relations are also not simple It is clear that factors other than retinal position influence fusion, to consider this aspect alone Thus, of elements in the two figures of a stereogram having the same relative position on the two retinas, some will "break," while

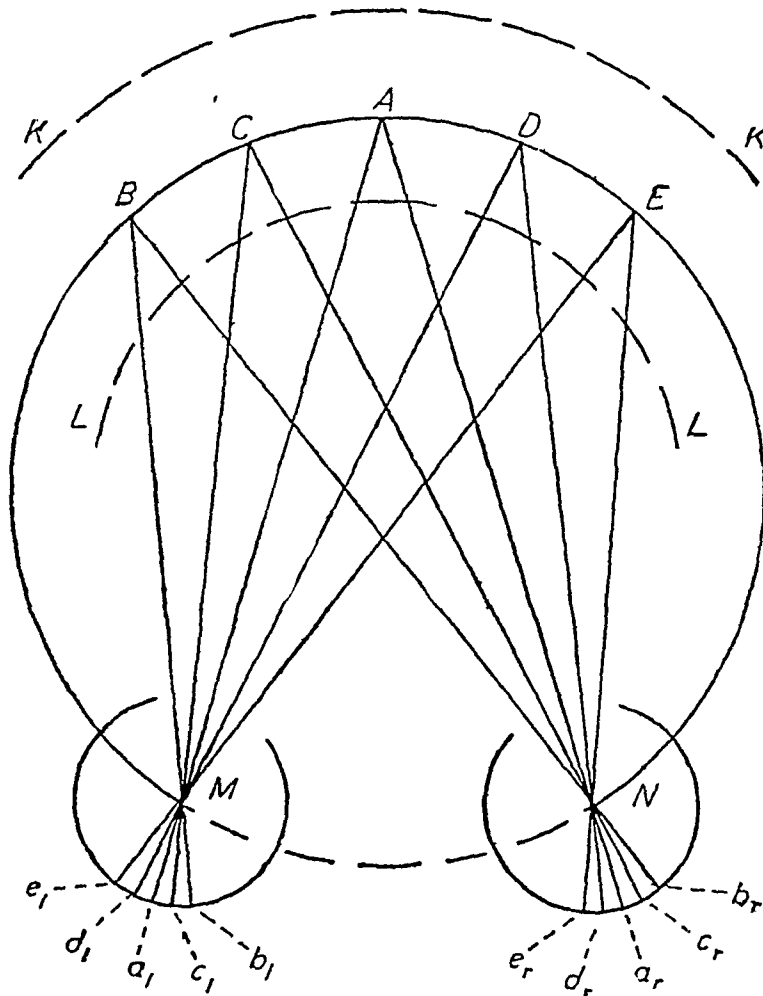


Fig 2—The horopter—a schematic drawing showing the Vieth-Müller circle and Panum's area

others remain fused under the stress of induced divergence; or convergence Size, complexity of form, brightness and foveal or extrafoveal position appear to be some of the determining factors From a consideration of these facts, it follows (a) that a purely anatomic definition of corresponding "points" cannot be satisfactory, and (b) that corres-

<sup>3</sup> Best, C H, and Taylor, N B The Physiological Basis of Medical Practice, ed 2, Baltimore, Williams & Wilkins Co, 1939, p 1656

ponding "areas" is a better term than "points,"<sup>4</sup> since fusion occurring without exact geometric correspondence is characteristic of the whole range of positions perceived as "single" and "near" or "far"

If one accepts the original, and most commonly accepted, criterion, that of singleness, the horopter is not a line but a band (Panum's area), shown in figure 2 between circles *K* and *L*. The horopter as a line would be a statistical construct representing the mean position of points in any section of the area. Criteria other than singleness have been proposed and other divisions of visual space experimentally determined. Ames, Ogle and Gliddon<sup>5</sup> cited Tschermak<sup>6</sup> as listing four criteria for determining the horopter. These are (1) the criterion of "median single vision", (2) the criterion of the "apparent frontal planes", (3) the criterion of constancy of "visual direction," and (4) the criterion of the "maximal differential sensibility of depth." The quotation marks indicate Tschermak's terminology.

The first of these criteria is the conventional definition, leading to Panum's area aforementioned. The second criterion leads to the *Kernfläche*, or *Kerzebene* of Hering,<sup>7</sup> the locus of points seen as equidistant with the fixation point. The third criterion was used by Ames, Ogle and Gliddon in determining the horopter by the grid nonius method. This is the locus of points seen by each eye as having similar directions.

Just as there are a number of statistical and subjective criteria, so there are numerous distances which may be arbitrarily termed thresholds, similarly, there are many surfaces which are of use in describing certain visual functions. Instead of the term "horopter," which is defined as the locus of points seen singly, it is suggested that one speak of surfaces and make use of two adjectives, one to describe the subjective and one to describe the statistical criterion for determining the threshold, 1. Phrases such as "50 per cent single surface," or "75 per cent equidistant surface," or "90 per cent equidirectional surface" would be far less confusing than the single term "horopter." Such operational terminology, which includes a description of how the surface was determined, would carry with it the implication that there are a number of related surfaces

4 Martin, E. G., and Weymouth, F. W. *Elements of Physiology*, Philadelphia, Lea & Febiger, 1928, p. 687.

5 Ames, A., Jr., Ogle, K. N., and Gliddon, G. H. Corresponding Retinal Points, the Horopter, and Size and Shape of Ocular Images, *J. Optic. Soc. America* **22**: 554, 1932.

6 Tschermak, A. *Optischer Raumsinn*, in Bethe, A., von Bergmann, G., Emden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1930, vol. 12, p. 894.

7 Hering, E. *Der Raumsinn und die Bewegungen des Auges*, in Hermann, L. *Handbuch der Physiologie*, Leipzig, F. C. W. Vogel, 1879, vol. 3, pt. 4, pp. 343-601.

## II EXPERIMENTAL METHODS AND STATISTICAL ANALYSIS OF DATA

The preceding section dealt with the geometric and statistical aspects of the threshold, the angle of binocular parallax ( $\eta$ ) and the horopter (the spatial locus of subjective equality). In the present section we shall discuss the experimental methods of assessing distance discrimination and the statistical technics of threshold determination.

As stated, binocular distance discrimination is dependent on slight differences between the two retinal images. Such differences can be produced (*a*) by two objects, the relative distances of which may be reported, or (*b*) by a stereoscope, which presents to the two eyes two slightly different pictures.

Since the threshold is affected by the conditions, a brief survey of the chief experimental methods follows.

The earliest measurement of binocular distance acuity by the rod technic is apparently that of von Helmholtz.<sup>8</sup> He placed three needles at a distance of 34 cm and found that a change of 0.25 mm in the position of the middle needle could be distinguished binocularly but not monocularly. Since von Helmholtz was interested only in demonstrating the superiority of binocular distance perception, he was content to record the threshold as "less than" 60.5 seconds. This point was stressed by von Kries.<sup>9</sup> The value of 60.5 seconds should, therefore, not be considered as a threshold, as has been done by some authors.

Brooksbank James<sup>10</sup> followed von Helmholtz but used only two rods. Howard<sup>11</sup> altered the James apparatus, and, with slight modifications, his test is still in use by the United States Army Air Corps. As used by Howard, the apparatus consisted of two rods separated by 6 cm, the central portions of which were seen through an aperture by the subject from a distance of 6 meters. The rods were exposed momentarily by a shutter, and the subject was required to tell whether the right rod was nearer or farther than the stationary left rod. Twenty judgments each were made for distance separations of the rods, increased by 5 mm steps, and the linear threshold was taken as the difference in distance for which 75 per cent or more of correct answers were obtained.

The final modification of the test was to make the movable rod controllable by the subject, who attempted to place it at the same distance as the standard rod. The average deviation for from one to ten settings is used as the threshold.

There are many tests based on the principle of two or more objects whose relative distances are judged. A few will be mentioned. Disks instead of rods were used as targets by Howard<sup>12</sup> and Updegraff.<sup>13</sup> A set of white-headed

8 von Helmholtz, H. Helmholtz's Treatise on Physiological Optics, translated by J. P. C. Southall, ed. 3, Ithaca, N. Y., Optical Society of America, 1925.

9 von Kries, J. Notes, in von Helmholtz,<sup>8</sup> vol. 3, p. 375.

10 James, G. I. B. On the Measurement of the Stereoscopic Visual Acuity, *Lancet* 1 1763-1766, 1908.

11 Howard, H. J. A Test for the Judgment of Distance, *Am. J. Ophth.* 2 656-675, 1919.

12 Howard, H. J. Judgment of Distance with Semaphores and a Screen at 100 Meters, *Arch. Ophth.* 48 461-474, 1919.

13 Updegraff, R. The Visual Perception of Distance in Young Children and Adults, *Studies in Child Welfare*, Iowa City, University of Iowa Press, vol. 4, no. 4, 1930.

pins mounted on a black surface was used by Davidson<sup>14</sup>. The subject was asked to determine which pin protruded farthest. Short exposure time was a feature of Hering's *Fallapparat*, in which the subject viewed through a rectangular tube a fine thread and a ball which fell either behind or in front of the thread. In some modifications of this test a bead is suspended on the thread as a fixation and comparison object. Litinskii<sup>15</sup> has recently used a similar method.

The second method, the stereoscopic, may be used in two forms. In one, the pictures presented to the two eyes differ in the separation of the various objects, such as letters. The subject judges the relative apparent positions of the objects, and his acuity is determined by the smallest difference which he can judge correctly. In contrast, a single variable stereogram may be used. In its simplest form the stereogram consists of two lines presented to each eye, in one pair of which the separation may be varied by the observer or the experimenter. When the separation of the two pairs is the same, most persons will see the fused images as two equidistant lines, if the separation of the variable pair is changed, the two lines will appear at different distances. In Howard's stereomicroscope<sup>16</sup> the subject controls the lateral position of one pair with a micrometer screw, and his task consists in setting the lines so that they appear equidistant. The well designed Pulfrich stereoscope<sup>17</sup> may also be used in this manner.

It has already been stated that unless the experimental conditions, the subjective criteria and the statistical standards are specified, and the effect of these conditions on the results are known, comparison of the thresholds obtained by different workers is meaningless. The following values must be regarded in this light, merely as recorded thresholds of distance discrimination, and cannot be further analyzed here. Von Helmholtz, as already noted, obtained a threshold of "less than" 60.5 seconds; Stratton<sup>18</sup>, one of 24 seconds, Bourdon<sup>19</sup>, one of 5 seconds, Crawley<sup>20</sup>, one of 23 to 20 seconds, Howard<sup>11</sup>, one of 18 to 136.2 seconds, Andersen and Weymouth<sup>21</sup>, one of 2 seconds, Frubose and Jaensch<sup>22</sup>, one of 2 seconds, and Langlands<sup>23</sup>, one of 1.6 to 5 seconds. If an average value must

14 Davidson, M. A Simple Device for Measuring Stereopsis, *Am J Ophth* **18** 356-359, 1935

15 Litinskii, G. A. The Rapidity of Depth Perception, *Vestnik oftal* **13**, 850-860, 1938

16 Howard, H. J. A Stereomicroscope, *Am J Ophth* **3** 417-421, 1920

17 Pulfrich, C. Ueber eine Prufungstafel fur stereoskopisches Sehen, *Ztschr f Instrk* **21** 249-260, 1901. Zeiss, C. Neue Prufungstafel fur stereoskopisches Sehen, 1908

18 Stratton, G. M. A Mirror Pseudoscope and the Limit of Visible Depth, *Psychol Rev* **5** 632-638, 1898

19 Bourdon, B. La perception visuelle de l'espace, Paris, Schleicher freres & Cie, 1902

20 Crawley, C. W. S. Stereoscopic Vision, *Brit J Photog* **52** 446-447, 1905

21 Andersen, E. E., and Weymouth, F. W. Visual Perception and the Retinal Mosaic. I. Retinal Mean Local Sign—Explanation of the Fineness of Binocular Perception of Distance, *Am J Physiol* **64** 561-594, 1923

22 Frubose, A., and Jaensch, P. A. Der Einfluss verschiedener Faktoren auf die Tiefensehscharfe, *Ztschr f Biol* **78** 119-132, 1923

23 Langlands, N. M. S. Reports of the Committee upon the Physiology of Vision. IV. Experiments on Binocular Vision, Medical Research Council, Special Report Series, no 133, London, His Majesty's Stationery Office, 1929

be given, that of 2 seconds suggested by Duke-Elder<sup>24</sup> seems not far wrong. The minimum requirement for service in the Army Air Corps is approximately 10 seconds, but as actually applied it varies widely.

The final step in distance discrimination is the statistical analysis of the data. This varies with the experimental method of determining the threshold. The three fundamental psychophysical methods, dating from Fechner,<sup>25</sup> have been listed by Boring<sup>26</sup> as follows: (a) the method of limits (minimal changes), (b) the method of right and wrong cases (constant method), (c) the method of average error (production method). The last two methods have been commonly used in determination of distance discrimination.

The method of average error as applied to the rod technic may be described briefly. A fixed standard and a movable comparison rod controlled by the subject are provided. The task is to place the comparison rod, initially set obviously far or near, at the same distance as the standard. The recorded settings of the comparison rod furnish a series of estimates of the position judged equidistant and may be arranged as a frequency distribution. Such a distribution may be described by a mean, or average estimate and a standard deviation, or variability of the estimates, about this mean. The mean is the position of subjective equality,  $E_s$ , the standard deviation indicates the accuracy with which the particular subject groups the settings about the  $E_s$ , and since some function of this scatter has generally been taken as the threshold, the simplest solution is to take the standard deviation itself as the threshold.

In the constant method a standard rod is also used, but the movable rod is successively placed at various points within the range corresponding to that obtained with the method of average error, and reports are required of the subject regarding its position relative to the standard. Several technical points in this method affect the results obtained, and hence require consideration. The most important are the time of exposure, the position and number of the stations and the categories of answers required.

The time of exposure controls fixation. If short, fixation may be restricted to a particular point, a matter of importance in determining the horopter. The stations, or fixed values of the stimulus, should lie within the range that would include all the settings of the average error method. The extremes should be far enough apart to provide clear contrast, but not nearer than 5 per cent to either end. A conventional number of stations is five, but smaller numbers (four, or even two) have been successfully used and possess certain advantages if normality of distribution need not be checked.

The use of a category of "equal" or "doubtful" answers has been condemned by several workers because of the marked effect on the threshold of the variability in attitude toward these answers. The two category report ("near" and "far") seems preferable and has been used by us.<sup>27</sup>

If the percentage of "near," or "far," answers obtained with the two category report are plotted on the y axis against the stimulus value of the stations on the x axis, a cumulative, or integral, curve is obtained which crosses its mirror image obtained from the contrasting answer at 50 per cent. From either curve, since they contain the same information, can be obtained the median (or mean, if the

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<sup>24</sup> Duke-Elder, p. 1078

<sup>25</sup> Fechner, G. T. *Elemente der Psychophysik*, Leipzig: Breitkopf & Härtel, 1860.

<sup>26</sup> Boring, E. G. *Sensation and Perception in the History of Experimental Psychology*, New York, D. Appleton-Century Company, Inc. 1942, pp. 37-41.

<sup>27</sup> Weymouth, F. W. and Hirsch, M. J. Unpublished report.



curve is not skew) and the standard deviation. This is most easily accomplished by some sort of transformation of the percentage scale which will make the regression of percentage on the value of the stimulus linear if the basic distribution is normal. The frequency ratio, or probit method, developed by Bliss<sup>28</sup> for biologic assay, is well adapted to this purpose. Tables for transforming percentages to probits are available (Fisher and Yates<sup>29</sup>), the weighting of observations and the standard errors of the parameter estimates are, unlike those of the phi-gamma method, not matters of dispute. The method is time consuming but not more so than the classic phi-gamma method.

Having discussed the two most commonly used and appropriate methods for determining the threshold of distance discrimination, it may be well to consider the retinal counterparts of these procedures. These relations are suggested in figures 3 and 4. Figure 3 represents the situation when the method is that of average error. The seven stations of the movable rod are  $B_1$  through  $B_7$ ; the relative frequencies of the settings at these points are represented by the heights of the lines erected above  $B'_1$  through  $B'_7$ . The tops of these ordinates are connected, suggesting the shape of the distribution if a large number of observations had been made. This approximately normal distribution has a mean at  $B'_4$  and a standard deviation represented by the distance  $B'_4-B'_6$  or any other of the equal spaces diagramed. The total range of six standard deviations might, at a distance of 6 meters, amount to 175 mm.

It will be seen from figure 3 that if the subject is fixating rod  $A$  and adjusting  $B$  for equidistance, four points on the two retinas must be considered, the images of  $A$  and  $B$  on each retina. Since  $A$  is fixated, its image on the left retina,  $a_l$ , and its image on the right retina,  $a_r$ , will fall on the two foveas, the primary corresponding points. The image of  $B$  on the left retina is always  $b_l$ . The entire distribution of point  $B$  is projected greatly minified on the retina about  $b_l$ . It must again be emphasized that the scale of the diagram is greatly distorted, for the conditions suggested, the separation of  $a_r$  and  $b_l$  would be about 0.2 mm, and the range of the retinal distribution,  $b_1b_7$ , 0.0005 mm. This distribution, marking the actual points on the retina the stimulation of which gave rise to perceptions of a rod equidistant with  $A$ , is, like its external counterpart, normal and may be described by a mean,  $b_4$ , and a standard deviation,  $b_4b_6$ .

It is usually stated that point  $b_4$  corresponds to point  $b_1$ ; but it is immediately apparent that  $b_4$  is a statistical concept and not a "point." A more important view is that 68 per cent of observations judged to be equidistant would fall between  $b_3$  and  $b_5$ . The point  $b_4$  may not have

28 Bliss, C. I. The Calculation of the Dosage Mortality Curve, *Ann. Applied Biol.* 22:134-167, 1935, The Comparison of the Dosage Mortality Data, *ibid.* 22:307-333, 1935.

29 Fisher, R. A., and Yates, F. *Statistical Tables*, Edinburgh, Oliver & Boyd, 1938.

the position suggested by the geometric construction, and  $B'_4$  may not be at the same distance as  $A$ , or instrumental equality,  $E_1$

Thus, for many observers,  $E$ , proves to be nearer or farther than  $E_1$ . In addition to the random differences which might be expected, especially with small samples, many observers show a systematic and significant difference between  $E$ , and  $E_1$ . The causes underlying this are complex. The actual retinal images and their separations are, of course, positioned in accordance with the rules of geometric optics. The

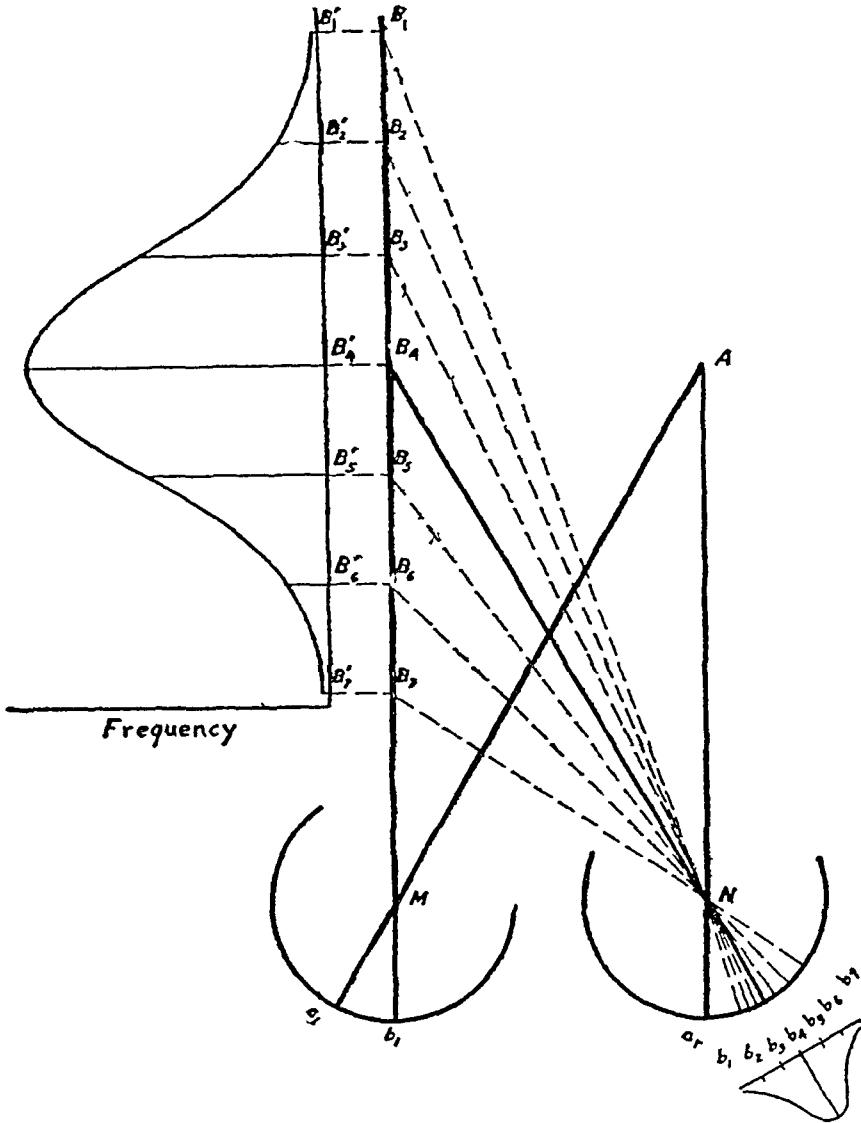


Fig. 3—Relation of statistical measures of threshold of distance discrimination to retinal pattern determined by the statistical method of average error

relative size of these images in the two eyes is affected by differences in the axial lengths of the eyes if emmetropic, or differences in length combined with the action of lenses in corrected ametropia. In addition, there is generally a difference in the space value of equal distances on the nasal and the temporal portions of the retina, and perhaps an over-all difference in "grain" between eyes. As a result, there often occurs a

difference in apparent image size, or aniseikonia, and this displaces the  $E_s$  by producing a retinal disparity in the case of external objects which are separated by equal visual angles

Figure 4 illustrates the relations with the constant method. The conditions are similar to those of figure 3 except that the answers are "near" or "far" for each exposure of the rods. The curves which should be compared with the previous diagram represent the percentages of "near" and "far" answers at each of the stimulus stations, here located at separations of one standard deviation.

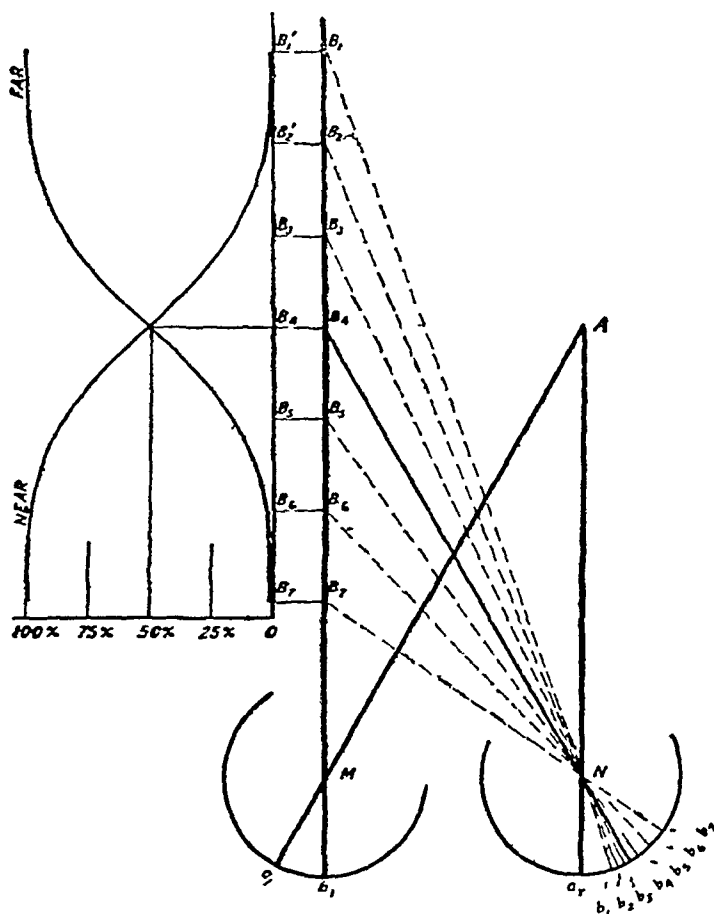


Fig 4—Relation of statistical measures of threshold of distance discrimination to retinal pattern determined by the constant method

These curves represent the cumulative, or integral, form of the normal curve. Thus, when the rod is at  $B_7$ , there will be 0.1 per cent of "far" answers and 99.9 per cent of "near" answers. On passing to  $B_6$ , one standard deviation further away, there will be an increase to 2 per cent of "far" answers and a decrease to 98 per cent of "near" answers. When the rod is at  $B_4$  the "far" answers will have increased to 50 per cent and the "near" answers will have decreased to 50 per cent. Thus, by summing from opposite ends, the "fars" from the near end and the "nears" from the far end, one obtains the cumulative normal

curves shown in the figure. As in the preceding example, the percentage distribution curve of the positions of the stimulus rod can be transferred in greatly reduced size to the retina and expressed in retinal distances.

It is possible now to define certain terms. In figure 3 the curve was so drawn that the mean, the position of subjective equality,  $E_s$ , coincides with the position of instrumental equality,  $E_i$ . This, as previously stated, does not always occur. These points may be transferred to the retinas; the two images of  $A$  fall on the foveas,  $B_4 = E_i$  will be imaged at  $b_1$  on the left retina, and at  $b_4$  on the right retina. This may be called the theoretic corresponding point of  $b_1$ . The image of  $E_s$  will be the functional corresponding point of  $b_1$ , these two points will coincide in the rare cases in which  $E_s$  and  $E_i$  coincide, or they may differ appreciably. There is obviously an area about the functional corresponding point which represents lesser correspondence, and the best measure of the size of this area is the standard deviation,  $S_x$  of the normal curve.

We have defined aniseikonia' as an apparent difference in image size, if the image size is considered as the length of the line connecting the images of  $A$  and  $B$  on either retina, it will be seen that when  $E_i$  and  $E_s$  fail to coincide by more than random error it is proof of aniseikonia.

It has been shown that threshold data contain information on two sensory characteristics, the position of subjective equality,  $E_s$ , a systematic "error" of the observer associated with aniseikonia, and a dispersion, or true, threshold, indicating the consistency of judgment. Obviously, any method of calculation which does not yield these two values sacrifices part of the information. The most commonly used threshold is the "average error" of the settings of the Howard apparatus. This is the mean deviation about the position of instrumental equality, which is larger because of the inclusion of  $E_s$ , but cannot be further analyzed. A more satisfactory measure is the root mean square error,  $R_{mse}$ , a statistical measure of which the standard deviation is a special case. The  $S_x$  is a measure of dispersion around the  $E_s$  or mean of the distribution; the  $R_{mse}$ , a measure of dispersion around the  $E_i$ . The relations are indicated in the following formula:

$$R_{mse} = \sqrt{E_s^2 + S_x^2}$$

While a single statistical measure presents possible advantages for a rough screening test, it should be clear that by its use much information is lost. The  $E_s$  is a measure of retinal functional correspondence, while the  $S_x$ , or threshold, is a measure of dispersion and, hence, of the variability of the individual subject. From the practical point of view, a high  $E_s$  may be corrected by the use of "size lenses" whereas the subject's characteristic variability of judgment cannot be altered. It would seem that if binocular acuity is worth measuring, it would be desirable to obtain all possible information.

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## DISTANCE DISCRIMINATION

### II Effect on Threshold of Lateral Separation of the Test Objects

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**I**N THE current tests for distance discrimination based on the technic of Howard,<sup>1</sup> the movable and the comparison rods are separated laterally by 6 cm. Howard did not give his reasons for selecting this value, it may have been with the intention of simplifying the geometric relations on which the calculation of the angle of binocular parallax is based. The average interocular distance is approximately 6 cm, and in Howard's figures the lines joining the eye and the rod on the same side are parallel.

#### PRESENT INVESTIGATION

The present experiment was designed to determine the effect on the threshold of the lateral separation of the targets. The centers of the test objects were separated laterally by distances of 2, 4, 8, 16 and 32 cm, since the subject was seated 17 meters from the test objects, the angular values of the separations were, respectively, 4'3", 8'5", 16'11", 32'21" and 64'42". Assuming Gullstrand's value of 17.05 mm as the distance of the nodal point from the retina, the retinal separations of the images were 20, 40, 80, 160 and 320 microns, respectively. Accurate fixation on one of the rods was maintained, and it may be assumed that its image fell on the foveas of the two eyes. The image of the other test object fell on pairs of corresponding areas, located at the distances just mentioned, lateral to the fovea.

*Methods*—Accurate fixation of one of the test objects was desired, combined with an exposure time sufficiently short to preclude the possibility of any ocular movement. It was further desirable to have the apparatus similar to that of Howard, so that results obtained might be of use in the design of testing apparatus. Exposure of the targets for less than 0.1 second would safely eliminate the possibility of ocular movements, since Erdman and Dodge<sup>2</sup> found the reaction time

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The apparatus here described was constructed and the experiments were performed with funds made available by the Air Material Command, Wright Field, Dayton, Ohio

1 Howard, H J. A Test for the Judgment of Distance, *Am J Ophth* 2: 656-675, 1919

2 Erdman, B, and Dodge, R. *Psychologische Untersuchungen über das Lesen*, Halle, Max Niemeyer, 1898

of the ocular muscles to be between 0.162 and 0.170 second. The method was fundamentally that of Hering's falling ball apparatus, more recently used by Litinski<sup>3</sup>

The subject was seated 15 meters from a partition. An aperture 19 by 54 cm in the partition permitted a view of a milk glass screen 3 meters further from the observer, illuminated to the same level as the partition and other walls in the field of view. A small red spot projected on the screen served as a fixation point. Between the partition and the screen, and above the field of view, were two tracks parallel to the long axis of the room and adjustable as to separation and height above the aperture. On these tracks ran two cars from which the test objects, metal rods 6 cm long and 0.6 cm in diameter, were released. A magnetic release controlled by a switch in the hand of the subject dropped the two rods simultaneously when the subject had fixated the red spot and was otherwise ready. The tracks and cars were so oriented that one rod was at a fixed distance (17 meters) and passed down directly in front of the red fixation point, which was automatically turned out at the moment that the rod was released. The other rod fell at a determined distance to the right or the left of the reference rod and at stations nearer or farther, as desired. The time relations were determined by the height of the tracks above the top of the aperture and in the present experiment were such that 0.104 second elapsed from the moment that the bottom of the rods appeared below the top of the aperture until the top of the rods disappeared behind the bottom of the opening. The entire rod was present in some part of the field for 0.05 second, it took the rod 0.03 second to pass a given point in the field at the top, and 0.02 second at the bottom, of the aperture.

The constant method was used with two categories of answers. The parameters were calculated by the probit method of Bliss and Fisher,<sup>4</sup> and the standard deviation was used as the threshold. The constant method is well known, a discussion of the reasons for its selection, details of its application and references are given in the first paper of the present series on distance discrimination.<sup>5</sup> Here it will suffice to point out the following aspects.

Forcing the answers into two categories, "near" and "far," eliminates the differences in subjects or in the reports of the same subject at different times with respect to the "equal" or "uncertain" judgments, and thus tends to stabilize thresholds. The probit method is superior to the phi-gamma method in the statistical rationale of its weighting and of its standard errors. The adoption of the standard deviation as the threshold (it will be called "threshold" in the remainder of the paper) utilizes the most stable measure of the distribution. This method is valid only for normal distributions, but, unlike the phi-gamma technique, presents a test by which abnormal distributions may be rejected. It is equivalent to using the distance from the 50 per cent point to either the 16 or the 84 per cent point or their average, as the threshold. The threshold is more stable than that based on the 25 or the 75 per cent point.

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3 Litinski, G. A. The Rapidity of Depth Perception, *Vestnik oftal* 6: 850, 1938.

4 Bliss, C. I. The Calculation of the Dosage Mortality Curve, *Ann Applied Biol* 22: 134-167, 1935. Fisher, R. A., and Yates, F. *Statistical Tables*, Edinburgh, Oliver & Boyd, Inc., 1938.

5 Hirsch, M. J., and Weymouth, F. W.: Distance Discrimination. I. Theoretic Considerations, *Arch Ophth*, this issue, p. 210.

Since the choice of stations affects the standard error of the threshold, care was taken to select 4 stations such that both the extreme near and far positions yielded between 80 and 90 per cent of correct answers. This selection was guided by an exploratory series of 10 trials at each of a number of stations. After the 4 stations were selected, 30 observations were made at each station, so that each threshold in this series is based on 120 judgments.

Ten series of observations were made on each of 4 subjects. Each series took about one-half hour, and not more than 2 series were made on any one day. With fixation on the right or the left rod, each of the five lateral separations previously mentioned were used. A random order, which was different for each subject, was used so that effects of practice and fatigue might be minimized for the group data.

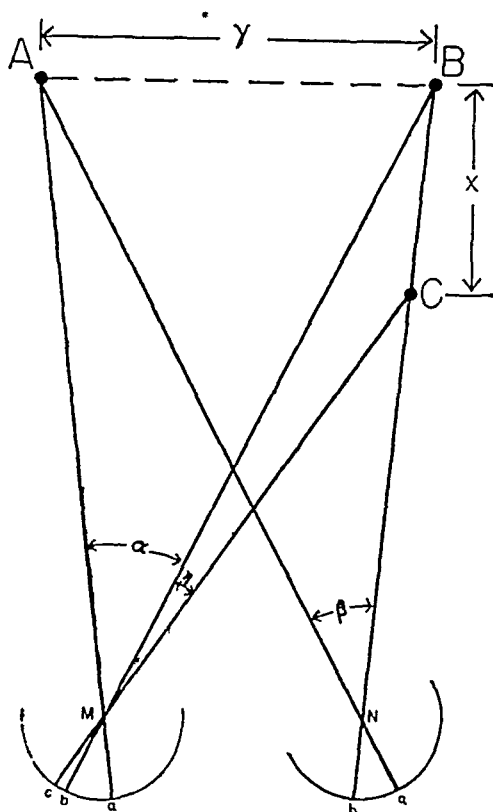


Fig 1—Schematic diagram of relations involved in binocular parallax

The relations involved in binocular parallax are presented schematically in figure 1. To make these relations apparent, since the actual angles are minute, the scale of the diagram has been greatly distorted. The distance  $NC$ , for example, is actually fifty or one hundred times as great as  $BC$ , while  $MA$  is one thousand times as great as  $Ma$ .

The object  $A$  is assumed to be point fixated. When the movable rod is at  $B$ , at the same distance as  $A$  from the eye, the angles  $\alpha$  and  $\beta$  are equal. If, now, the movable rod is advanced to point  $C$ , the distance  $r$  being the threshold, then angle  $\eta$  is the retinal disparity, or binocular parallax. The greater the distance  $y$  separating the test objects, the greater the angle  $\alpha$ . The present experiment is concerned with the effect of the size of angle  $\alpha$  on the threshold,  $\eta$ .

## RESULTS

The 40 thresholds, each based on 120 judgments and expressed in millimeters, are presented in table 1, together with the averages for the 4 subjects and the angle of retinal disparity  $\eta$  based on these means. An analysis of variance on these thresholds was carried out to see what elements of the experiment had significant effects; the results are shown in table 2. There are three factors in the design of the experiment: the

TABLE 1—Thresholds ( $S_e$ ) for Four Subjects Determined Under Ten Conditions

Fixation	Condition		Threshold, Mm					Angle of Retinal Disparity ( $\eta$ ) for Average, Sec
	Angular Separation of Targets, Sec		Subject 1	Subject 2	Subject 3	Subject 4	Average	
Right	3,882		341 18	277 80	238 86	642 51	375 09	17 4
Right	1,941		241 28	248 16	194 90	218 73	225 77	10 5
Right	971		182 10	361 81	153 59	221 87	229 84	10 7
Right	485		246 10	284 71	133 31	385 51	262 41	12 2
Right	243		280 23	212 35	236 97	583 91	328 36	15 2
Left	243		374 43	540 07	232 80	537 62	421 23	19 5
Left	485		259 12	315 29	159 01	757 26	372 67	17 3
Left	971		300 88	179 96	168 48	240 46	222 44	10 3
Left	1,941		351 80	203 65	155 03	251 63	240 53	11 2
Left	3,882		383 42	297 69	296 56	339 38	329 26	15 3

TABLE 2—Sources of Variation in Thresholds of Distance Discrimination

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio, $F$	5% Level	1% Level
Separation of rods (I)	148,365	4	37,091	2 83	3 3	5 4
Fixation (F)	10,846	1	10,846			
Subjects (S)	245,916	3	81,972	6 26	3 5	6 0
IF	35,463	4	8,866			
IS	152,792	12	12,733			
FS	6,645	3	2,215			
IFS (error)	157,251	12	13,104			
Total	757,278	39				
Separation (I)	148,365	4	37,091	3 27	2 7	4 0
Fixation (F)	10,846	1	10,846			
Subjects (S)	245,916	3	81,972	7 22	2 9	4 5
All interactions (error)	352,151	31	11,360			
Total	757,278	39				

separation of the rods ( $I$ ), fixation with the right or with the left eye ( $F$ ) and subjects ( $S$ ). Using the second order interaction of these three factors ( $IFS$ ) as the error, only the difference between subjects is significant at the 1 per cent level. This is, of course, neither surprising nor important for our present purpose. Since none of the first order interactions is even as large as the mean square of the error, it is possible to combine all interactions into a single error term. On this basis, the separation is significant to about the 2 or 3 per cent level, but fixation is still without significance.



These findings justify two conclusions 1 The separation of the rods has a significant effect on the thresholds, an effect which would probably have been clearer had more subjects been used This point will be discussed in more detail shortly 2 There is no significant difference between fixation on the right and that on the left Accordingly, the eight values (4 subjects and two fixations) for each separation have been combined and are presented in table 3 as means, together with the binocular parallax in seconds, and as a percentage of the angle of separation of the rods ( $100 \eta/a$ ) Beside the average thresholds, the variability of the thresholds must also be considered The standard deviation based on the eight values have been calculated for each of the five separations, and these are given in table 3 and are represented graphically as vertical bars above and below the average thresholds shown in figure 2 It is at once apparent that those separations which give the smallest thresholds also show the least variability The thresholds obtained at separations of 971 and 1,941 seconds are less

TABLE 3—Average Thresholds for Five Retinal Separations

Angular Separation of Targets ( $\alpha$ ), Sec.	Average Threshold, Mm	Standard Deviation, Mm	$\eta$ Sec	$100 \eta/a$
243	374.80	156.77	17.39	7.16
485	317.54	195.17	14.73	3.04
971	226.14	72.58	10.49	1.08
1,941	233.15	57.76	10.82	0.56
3,882	352.18	125.35	16.34	0.42

variable than those at other points to the 5 per cent level, and in some comparisons to the 1 per cent level, of significance

These results agree with the reports of the observers who said that judgments were difficult at both the least and the greatest separations All thresholds tend, in the present experiment, to be large, since the time that any particular point of the retina was exposed to the image of the falling rod was only 0.02 to 0.03 second A number of workers, including Cobb and Moss<sup>6</sup> and Graham and Cook,<sup>7</sup> have shown that acuity falls with shortened exposure, and it is probable that distance discrimination parallels visual acuity in this respect Possibly the movement also reduced acuity<sup>8</sup> Difficulty at the greatest separation might result from the reduced acuity at the extrafoveal point occupied

6 Cobb, P. W., and Moss, F. K. Four Fundamental Factors in Vision, *Tr. Illum. Engin. Soc.* **23**: 496-506, 1928

7 Graham, C. H., and Cook, C. Visual Acuity as a Function of Intensity and Exposure-Time, *Am. J. Psychol.* **49**: 654-661, 1937

8 Ludvig, E. Visibility of the Deer Fly in Flight, *Science* **105**: 176-177 (Feb. 14) 1947

by the unfixed image, or from the comparison of widely separated images. Weymouth and others<sup>9</sup> found that at 1 degree from the fovea visual acuity was reduced to 60 per cent. Difficulty at the least separation is less expected, since comparison might be thought to be easier. A closer scrutiny of the relation of the images, however, shows that their centers are separated by only 4 minutes and their inner margins by about 3 minutes. Since the rods are in motion and their images are of short duration, this small separation may scarcely have exceeded the effective resolving power of the eye and have justified the feeling "that the rods got in each other's way."

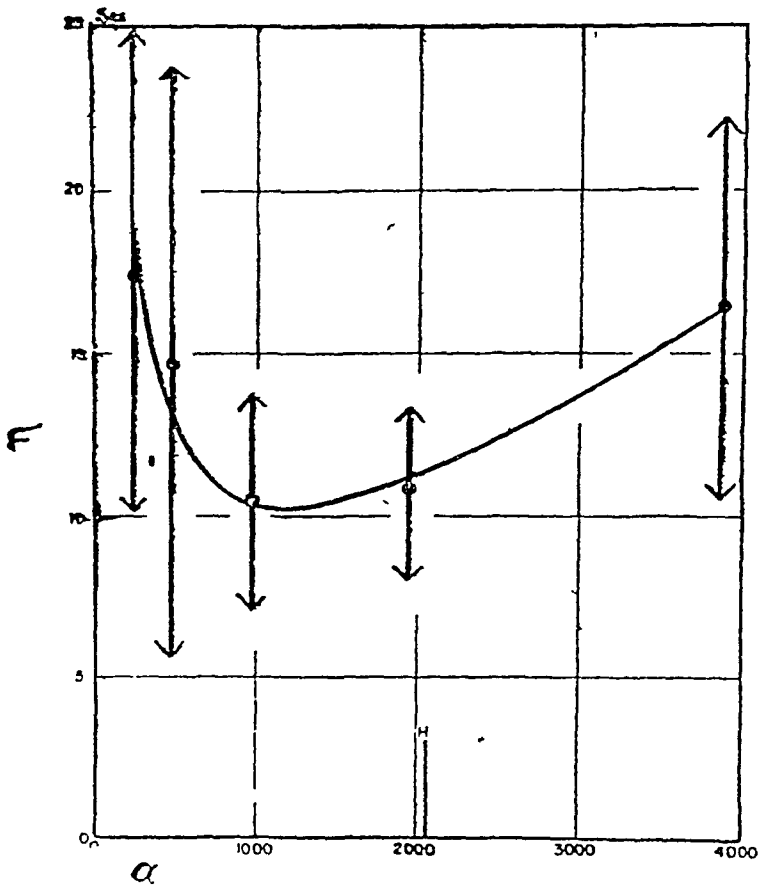


Fig 2—Effect of angular separation ( $\alpha$ ), expressed in seconds, on threshold ( $\eta$ )

It is probable that the minimum point (fig 2) for the threshold is a compromise between the increasing threshold as the image departs from the fovea and the difficulty of resolving the images of the two rods at the smallest separations.

There are few data available in the literature for comparison in experiments in which the separation of the rods was varied. Andersen

<sup>9</sup> Weymouth, F W, Hines, D C, Acres, L H, Raaf, J E, and Wheeler, M C. Visual Acuity Within the Area Centralis and Its Relation to Eye Movements and Fixation, *Am J Ophth* 11:947-960, 1928

and Weymouth,<sup>10</sup> working at 2 meters, used two separations giving angular values of 4,125 and 1,547 seconds, corresponding roughly to the two largest separations used in the present work. Although, owing to a difference of conditions, the thresholds cannot be compared directly, the limen at the greater separation was about 17 times that at the lesser, in the present work, the ratio of the two largest separations was only a little greater, i. e., 2.2. As far as these data go, they are in accord with the present findings.

Langlands,<sup>11</sup> also under conditions not permitting comparison with the present thresholds, studied the effect of separations of 0.5, 1, 2, 3 and 4 degrees. Over this range the threshold increased almost linearly with increase of separation. This observation agrees with our findings at comparable distances and indicates a continued increase of threshold to about four times the largest separation here studied.

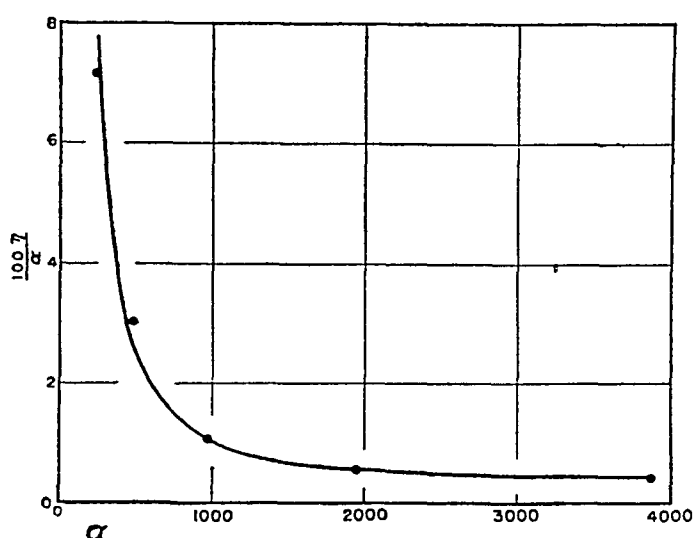


Fig. 3—Effect of angular separation ( $\alpha$ ), expressed in seconds, on threshold, expressed as a per cent of the separation ( $100\eta/\alpha$ )

The minimum point of the curve of threshold on separation (fig. 2) clearly lies between 971 and 1,941 seconds, but the type of relation did not prove easy to fit, and the smooth line of the figure was derived indirectly, in a manner later to be described.

In addition to the direct relation of the threshold to the separation, the relative threshold may also be considered. In figure 3,  $100\eta/\alpha$ , or  $\eta$  as a per cent of  $\alpha$ , has been plotted on  $\alpha$ , the angle of separation. On

10 Andersen, E. E., and Weymouth, F. W. Visual Perception and the Retinal Mosaic. I. Retinal Mean Local Sign—An Explanation of the Fineness of Binocular Perception of Distance, *Am. J. Physiol.* **64**: 561-594, 1923.

11 Langlands, N. M. S. Reports of the Committee upon the Physiology of Vision. IV. Experiments on Binocular Vision, Medical Research Council, Special Report Series, no. 133, London, His Majesty's Stationery Office, 1929.

this relative' basis, the threshold falls continuously without a minimum, in a manner suggesting a hyperbolic relation. The asymptote toward which the relative threshold is tending proves to have a value of about 0.35, and by shifting the origin by this amount the curve is well fitted by a hyperbola having the formula.

$$\frac{100\eta}{a} = \frac{79,440}{a^{1.658}} + 0.35$$

From this, the curve in figure 3 has been drawn

Working from this basis, the formula

$$\eta = \frac{794.4}{a^{0.688}} + 0.0035a$$

is obtained, and from this the curve in figure 2 was calculated

The orderly behavior of the relative threshold, falling from 7.16 to 0.42 per cent of the separation of the rods is a fact of obvious importance in the interpretation of experimental results, although this element has been generally disregarded.

On the basis of these data, the optimum separation of the rods would be approximately 19 minutes (1,140 seconds). At a distance of 6 meters, as the Howard apparatus is commonly used, this value would correspond to 33 mm, or about one-half the usual separation of 60 mm. Under the most favorable conditions the threshold might be expected to be reduced by about 12 per cent if a separation of the rods of 33 mm was used, instead of the customary 60 mm.

#### SUMMARY

The effect of the separation of the rods on the threshold of distance discrimination was studied for five separations, ranging from 4 to 64 minutes.

The apparatus used employs the principle of Hering's *Fallapparat* and was designed to permit accurate fixation and to prevent ocular movements during observations. Because of the short exposure, the thresholds are rather large, and binocular parallax threshold did not fall below 10 seconds.

Over the range studied, the effect of separation is significant and systematic. The threshold is at a minimum at a separation of about 19 minutes and rises sharply at lesser, and more slowly at greater, separations.

In the design of apparatus and in the interpretation of experimental results, the dependence of the threshold on separation of the targets as well as other features of the stimulus pattern must be considered.

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## SODIUM SULFACETIMIDE IN OPHTHALMOLOGY

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**I**NFECTION of the conjunctiva and the ocular adnexa has long been a source of distraction to the ophthalmologist, the bacteriologist and primarily the patient. In the era before bacteria were discovered the ophthalmic textbooks contained no specific admonitions as to treatment with the exception of the statement that when frank pus was noted heat in various forms relieved the irritation and at times caused pointing, opening and drainage of the abscess.

With the advent of modern knowledge of sepsis, smears and cultures of material from the conjunctival sac, the meibomian glands and the ciliary follicles were made. An enormous amount of laboratory work was accomplished and much appeared in the literature. It was found early that smears of material taken with a cotton applicator were not efficient as many of the organisms were invaders of the tissue cells and few appeared on the surface. A method of scraping the conjunctiva with a platinum spatula yielded more evidence of the offending organism.

Two factors of importance must not be overlooked. First many infections were self limiting, that is, because of natural defense mechanisms the infection cured itself without outside intervention. Second, human nature being what it is the patient rarely consulted the ophthalmologist early in the course of the disease, so that by the time smears and cultures were made the amount of mixed infection (that is, infection caused by organisms other than the original one causing the disease) so obscured the picture that specific treatment was impossible.

In the next period antiseptics used for general infections were modified in such a way that injury to the delicate epithelial cells no longer prohibited their use in the conjunctival sac. It was found that silver preparations, while moderately efficacious, were often irritating and might cause argyrosis. The silver protein preparations had the defect last mentioned and, in addition, were excellent culture mediums. The use of certain specific drugs such as ethyl hydrocupreime ("optochin"), zinc sulfate and copper sulfate also had drawbacks. Ethyl

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hydrocupreine was painful to use, although it killed the pneumococcus Zinc sulfate, while it had no bacterial effect in vitro, certainly was of benefit in chronic angular conjunctivitis due to *Haemophilus duplex* (Morax-Axenfeld bacillus), but other organisms were not affected Copper helped trachoma, but mechanical expression was also necessary In use of the aforementioned drugs and those to follow the fact that only the surface cells were being treated must not be lost sight of

Use of mercurial preparations has two important drawbacks (1) Sensitivity to mercurial preparations is widespread, and (2) preparations concentrated enough to be bactericidal could not be obtained from the manufacturer or had not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association The aforementioned solutions were all aqueous, and antiseptics dissolved in phenol or alcohol are deleterious to the epithelium and other tissue cells

Additional experimentation and therapy followed the discovery of the sulfonamide drugs The 5 per cent ointment prepared for ophthalmic use was found not to be very efficacious, in addition, there were many reports of sensitivity The sodium sulfanilamide could be dissolved only in 2 per cent solution, and little could be expected of such a weak solution

Penicillin used locally, either in solution or in ointment form, is marvelous when penetration is at its maximum, and certainly when given intramuscularly, as in cases of gonorrheal conjunctivitis, it is generally most efficient in curing the disease

The modern literature on bacteriologic investigations covering the past ten to twenty years is voluminous However, much of the important work has been reviewed and confirmed by a few eminent authorities It is my purpose, in order to save time and space, to bring to the attention, only the most important works As far back as 1897, Morax<sup>1</sup> and Axenfeld<sup>2</sup> independently taught much concerning the diplobacillus which bears their conjoined names Salle and his associates,<sup>3</sup> by substituting for the long-cherished phenol coefficient a method of growth of bacteria on living embryonic tissue contributed a logical criterion for the evaluation of an antiseptic Thompson and his colleagues<sup>4</sup> showed the efficacy of various antiseptics in removing organisms from the conjunctiva due to properties of the antiseptic.

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1 Morax, V Note sur un diplobacille pathogène pour la conjunctivite humaine, *Ann Inst Pasteur* **10** 337, 1896

2 Axenfeld, T Ueber die chronische Diplobacillen-Conjunctivitis, *Centralbl f Bakt* **1** 21, 1897

3 Salle, A J, McOmie, W A, and Shechmeister, I L New Method for the Evaluation of Germicidal Substances *J Bact* **34** 267, 1937

4 Thompson, R Isaacs, M L, and Khorazo, D A Laboratory Study of Some Antiseptics with Reference to Ocular Application *Am J Ophth* **20** 1087, 1937

such as disinfectant rate, highest concentration which is nonirritating to the conjunctiva influence of increased protein concentration on the disinfectant rate and toxicity of the antiseptic for leukocytes and for lysozym Nye<sup>5</sup> reported that of many antiseptics in aqueous solution iodine solution had the best rating Thygeson<sup>6</sup> in 1938 reviewed the literature on the treatment of conjunctivitis His work has been outstanding Subsequently, he<sup>7</sup> stated that sulfonamide compounds have revolutionized the treatment of trachoma, inclusion blennorrhea, lymphogranuloma venereum, gonorrheal conjunctivitis, streptococcic diphtheria of the conjunctiva (pseudomembranous conjunctivitis) and staphylococcic blepharoconjunctivitis Later, with Braley,<sup>8</sup> he reported good results from local treatment with sulfonamide compounds of over 500 patients with acute or chronic catarrhal conjunctivitis The history of modern therapy and chemotherapy was well outlined by Bellows,<sup>9</sup> whose work on absorption of the sulfonamide compounds in ocular tissues is well known to all In Brazil, Sales<sup>10</sup> studied the bacteriology of conjunctival secretions He analyzed the results of 5,369 examinations and found that the Koch-Weeks bacillus was the most prominent organism He also discussed seasonal and meteorologic influences P'an,<sup>11</sup> in a study of the absorption of sulfanilamide, had to use it over one hour in powder form to obtain a content of 44 mg per hundred cubic centimeters in the aqueous

In 1938 Dohrn and Diedrich<sup>12</sup> reported on the production of sulfacetimide (p-aminobenzene sulfonyl acetyl-imide) in the laboratory Welebir and Barnes<sup>13</sup> found that the drug was as effective in acid as in alkaline urine and therefore placed no value on the  $p_H$  of the

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5 Nye, R N Relative in Vitro Activity of Certain Antiseptics in Aqueous Solution, *J A M A* **108** 280 (Jan 23) 1937

6 Thygeson, P Treatment of Conjunctivitis, *Arch Ophth* **19** 586 (April) 1938

7 Thygeson, P Sulfonamide Compounds in Treatment of Ocular Infections, *Arch Ophth* **29** 1000 (June) 1943

8 Thygeson, P, and Braley, A E Local Therapy of Catarrhal Conjunctivitis with Sulfonamide Compounds, *Arch Ophth* **29** 760 (May) 1943

9 Bellows, J, in Wiener, M *Ophthalmology in the War Years*, Chicago, The Year Book Publishers, Inc, 1946, vol 1, pp 176-181

10 Sales, F J M Bacterioscopy of the Conjunctival Secretions, *Arg. Inst. Penido Burnier* **6** 390, 1942, Etiology and Pathogenesis Bacterioscopy of Conjunctival Secretions, *Rev. med. e cir. de São Paulo* **1** 105, 1941

11 P'an, S Y Ocular Absorption of Sulfonamide Derivatives After Local Application, *Proc. Soc. Exper. Biol. & Med.* **49** 384, 1942

12 Dohrn, M, and Diedrich, P *Albucid, ein neues Sulfanilsauerederivat*, München med. Wchnschr. **85** 2017, 1938

13 Welebir, F, and Barnes, R W The Use of Sulfacetimide in Bacillary Infections of the Urinary Tract, *J A M A* **117** 2132 (Dec 20) 1941

urine Czekalowski<sup>14</sup> demonstrated that sulfacetimide acts as a stimulus to polymorphonuclear leukocytes. Rosenthal<sup>15</sup> found that sulfacetimide differs from the acetyl sulfanilamide formed in the body as the acetylation occurs on the sulfonamide group and is therefore less toxic than sulfanilamide. Scott<sup>16</sup> advised use of a 10 per cent solution of sulfacetimide as a substitute for the Crede method of instilling a drop of 2 per cent silver nitrate in each eye of the newborn infant. Toland and Kornbluh<sup>17</sup> obtained excellent results in the prophylactic topical treatment of wounds. They observed no irritations or toxic symptoms due to the drug.

The local clinical use of a 30 per cent solution of sodium sulfacetimide was first reported by Dickson<sup>18</sup>. Under the auspices of the Ross Foundation for the Prevention of Blindness, in a trial period of six months of 11 953 cases of ocular injuries, there were only 7 instances of corneal ulcer while before the use of this drug 350 cases of corneal ulcer occurred in a three year period. Thus the preventive value is obvious. The rapid absorption of the drug into ocular tissue was attested by Robson and Tebrich<sup>19</sup>. They were satisfied that with the local use of 30 per cent sodium sulfacetimide the concentration in the conjunctiva, cornea, aqueous, sclera and even the iris was at its peak after fifteen minutes and that it was adequate after one hour. The work of Robson and Scott<sup>20</sup> provided evidence of the bactericidal action. Later Ginsburg and Robson<sup>21</sup> found that addition of a wetting agent increased the penetration of sulfacetimide into and through the cornea. They found that removal of the corneal epithelium increased the penetration as the cornea acts as a barrier. Kuhn<sup>22</sup> observed no cases of

14 Czekalowski, J. W. Studies on Stored Blood. VII. The Effect of Sodium Sulphapyridine, Albucid Soluble and Hydrogen Ion Concentration on Phagocytosis, *Edinburgh M. J.* **48** 405, 1941.

15 Rosenthal, S. M. Pharmacology of the Sulfonamide Drugs, *South M. J.* **35** 484, 1942.

16 Scott, G. I. The Effectiveness of Sulphonamides When Applied to the Eye, *Tr. Ophth. Soc. U. Kingdom* **62** 3, 1942.

17 Toland, J. J., and Kornbluh, I. Preliminary Report on Prophylactic Topical Use of Sodium Sulfacetimide, *Indust. Med.* **13** 946, 1944.

18 Dickson, R. M. Traumatic Ulcer of the Cornea with Special References to Coal Miners, *Brit. J. Ophth.* **26** 529, 1942. First Aid Treatment of Industrial Eye Injuries, *ibid.* **27** 544, 1943.

19 Robson, J. M., and Tebrich, W. Penetration and Distribution of Sodium Sulfacetimide in Ocular Tissues, *Brit. M. J.* **1** 687, 1942.

20 Robson, J. M., and Scott, G. I. Local Effectiveness of Sodium Sulphacetimide (Albucid Soluble) in Treatment of Experimental Ulcers of the Cornea, *Brit. M. J.* **1** 5, 1942.

21 Ginsburg, M., and Robson, J. M. The Effect of Detergent on the Penetration of Sodium Sulphacetimide (Albucid Soluble) into Ocular Tissues, *Brit. J. Ophth.* **29** 185, 1945.

22 Kuhn, H. S. Sodium Sulfacetimide Thirty per Cent in Ophthalmology, *Tr. Am. Acad. Ophth.* **50** 210, 1946.



sensitivity The drug compares favorably with penicillin as an anti-infective agent.<sup>23</sup> From Russia comes the report by Krasnov<sup>24</sup> that in 45 cases of serpiginous ulcer treated with sulfacetimide there were no perforations and that the remaining scars were very fine The 10 per cent solution was ineffective Sarkisov<sup>25</sup> had good results in treatment of gonorrheal ophthalmia in adults

In May 1946 I was supplied with a quantity of a 30 per cent solution of sodium sulfacetimide<sup>26</sup> It is said to be the only sulfonamide drug which can be prepared in such highly concentrated solution at the physiologic  $p_H$  of 7.4 I shall not give in detail the protocols of the clinical and laboratory experiments which have been accomplished during the past year I shall, however, indicate the type of experiments which were carried out and the results About 3,000 eyes with acute and chronic conjunctivitis were treated There were no reactions which could be considered either as a sensitivity or as an allergic reaction Three patients complained of burning, so severe it was necessary to stop the use of the drug In many cases of bilateral infection controls were carried out as follows (1) without medication, (2) with (a) 1 per cent silver nitrate and (b) 2 per cent silver nitrate neutralized with isotonic solution of sodium chloride, (3) with (a) 10 per cent and (b) 20 per cent mild silver protein U S P ("argyrol"), (4) with hexylresorcinol, 1 2,500, (5) with nitromersol N F ("metaphen"), 1 5,000 and (b) 1 2,500 nitromersol, (6) with ethyl hydrocupreine ("optochin"), 0.5 per cent (7) zinc sulfate, 0.5 per cent, (8) mercuric oxycyanide, 1 3,000, and, finally, (9) benzylkonium ("zephiran") chloride, 1 1,000 Smears and cultures were made in the early days of this work However, as the usual effects were noted, and these seemed to have little influence on the result of treatment, it was decided that these procedures were unnecessary In 365 eyes in which a foreign body was removed—from the lids, by simple wiping of the cornea or, when deeply embedded, by spudding out—a 30 per cent solution of sodium sulfacetimide was dropped in the eye for several days No infection occurred in any case The average mean periods of recovery for the various methods for all the cases of acute and chronic conjunctivitis were as follows without medication, seven days, with 1 per cent silver nitrate, six days, with 2 per cent silver nitrate, five days, with 10 per cent mild silver protein, eight days, with 20 per cent mild silver protein, seven and a half days, with hexylresorcinol, 1 2,500, five

23 von Sallmann, L Simultaneous Local Application of Penicillin and Sulfacetimide, *Arch Ophth* **32** 190 (Sept) 1944

24 Krasnov, M Treatment of Serpiginous Corneal Ulcers with Albucid, *Vestnik oftal* **23** 22, 1944

25 Sarkisov, S A Sulfacetimide in Gonorrheal Conjunctivitis of Adults, *Sovet med* **9** 24, 1945

26 The solution was supplied by the Schering Corporation, Bloomfield, N J

days, with nitromersol, 1 5,000, five days, with nitromersol, 1 2,500, four and a half days, with ethyl hydrocupreine, 0.5 per cent, four and a half days, with zinc sulfate, 0.5 per cent, five days, with mercuric oxycyanide, 1 3,000, seven days, with benzylkonium chloride, 1 1,000 eight days, and with 30 per cent sodium sulfacetimide, three days

Alexander Fleming's<sup>27</sup> comments concerning chemotherapy seem appropriate here

Local chemotherapy has been practiced since the days of Lister, but the underlying principles are even now little appreciated. These chemicals are said to possess this or that coefficient, and although this is perfectly true according to the tests employed, it generally has little bearing on their value as bactericidal agents in the human body.

As regards organisms such as the pyogenic cocci which are so intimately connected with ophthalmology, the chief defenses of the body are the phagocytic cells which pick up and destroy such bacteria after they have been opsonised by the blood or body fluids. It is easy to test the relative potency of a chemical to leucocytes and to bacteria by mixing the chemical in varying concentrations with suitably infected blood. The ferment lysozyme is seriously interfered with by a great many of the chemical antiseptics in common use.

In the past too much attention has been paid to the bactericidal action of chemical antiseptics, and better results might be hoped for if workers gave more care to the bacteriostatic action.

In my experience a 30 per cent solution of sodium sulfacetimide is an ideal antiseptic in cases of acute and chronic infections of the conjunctiva.

634 North Grand Boulevard

#### ABSTRACT OF DISCUSSION

DR PHILLIPS THYGESON, San Jose, Calif. Topical application of the sulfonamide drugs to the external eye can now be evaluated on the basis of about eight years' experience. The enthusiasm of earlier years has been tempered, but there is no doubt of the value of the treatment in many types of bacterial infections of the lids, conjunctiva and cornea. Overshadowed in treatment of some infections by the greater effectiveness of penicillin, the sulfonamide drugs have a much greater range of action on bacteria and can, in addition, be used against certain nonbacterial infections, such as trachoma, inclusion blennorrhea, and lymphogranuloma venereum, for which penicillin is ineffective.

There has been considerable criticism, particularly from dermatologists, of the indiscriminate use of the sulfonamide drugs, especially with minor infections, because of the frequency of sensitization, which could prevent the use of the drug in the treatment of a serious infection, such as pneumonia or meningitis, when it would be life saving. It would seem desirable, therefore, to have a sulfonamide drug with low or negligible sensitizing properties. Sodium sulfacetimide, the drug advocated by Dr. Mayer, would seem to have much to offer in this respect.

<sup>27</sup> Fleming, A., in Ridley, F., and Sorsby, A. Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940.

In my limited experience, sodium sulfacetamide in 30 per cent solution has been relatively nonirritating to the conjunctiva and cornea. Dr. Mayer has stated that no sensitization to the drug developed in his series of over 3 000 cases, in striking contrast to the frequency of sensitization to sulfathiazole, which, in my experience, has occurred in as high as 5 per cent of cases. The drug is not entirely free from sensitizing properties, however, Dr. A. E. Braley, of New York, reported a case of typical sensitization. Fortunately, there is a low incidence of cross sensitization among the sulfonamide drugs, and it is probable that sulfadiazine could be used with safety in a case of sensitivity to sulfacetamide. A cutaneous test with a sulfonamide-serum mixture before systemic use would seem to be indicated, however. Dr. Mayer reports an average mean period of recovery of three days in cases of acute and chronic conjunctivitis, as against a period of seven days in cases of the untreated disease. These figures are without much meaning unless further data are supplied as to the number of cases and the etiologic factors involved. I have no doubt that sodium sulfacetamide is effective in treatment of acute catarrhal conjunctivitis. I have grave doubts, however, of its value in many cases of chronic conjunctivitis when applied in solution since in a high proportion of cases chronic conjunctivitis is secondary to blepharitis which is not reached by the solution. The lid margins are never wetted properly with solutions, and only an ointment could be expected to maintain an effective concentration of the drug in a case of blepharitis. It must be remembered that the sulfonamide compounds, unlike penicillin, are not bactericidal, but are only bacteriostatic and require a definite time interval for action.

The value of sodium sulfacetamide in the prophylaxis of corneal infection after foreign bodies is of great interest. I can see no reason that this or similar sulfonamide substances should not eventually replace silver nitrate in the prophylaxis of ophthalmia neonatorum. In addition to preventing gonococcic infection the sulfonamide drugs might also be expected to control inclusion blennorrhoea.

What is now needed is a survey of ocular infections to determine the incidence of sulfonamide-resistant strains of bacteria. Such a study would be a great help in enabling ophthalmologists to employ topical sulfonamide therapy effectively.

Dr. Mayer has performed a real service in calling attention to the efficacy of this more recently developed sulfonamide drug and to its lack of sensitizing properties.

DR. EUGENE W. ANTHONY FULTON, N. Y. Dr. Mayer has given an excellent summary of the value of this drug, which is no doubt relatively new to most of us. It was introduced in Germany in 1938 but gained its great popularity in ophthalmology in Great Britain in 1941 and 1942. There it is commonly called "albucid." I spent two and a half years as ophthalmologist to one of the army hospitals in England during the war. When we arrived in late 1942, there were nine ophthalmologists in that theater, and the three most discussed words of that time were Duke-Elder, Colonel Vail and "albucid." During 1943, owing to the generosity of our hosts, we were invited to all the British ophthalmological meetings, both local and in London. We each spent two weeks at Moorfields Eye Hospital and visited many of the other ophthalmic hospitals of the country, including those at

Birmingham and Glasgow We found a great deal of enthusiasm for the new drug "albucid" It was soon obtained for our army on lend-lease from the British by the work of Colonel Vail and Brigadier General Duke-Elder Those of us in the stationary hospitals found it to be the best available drug for the conditions that Dr Mayer has mentioned It was used prophylactically in ocular wounds of all battle casualties and its instillation was to be routine in cases of gas casualties

With the advent of penicillin in 1944, the use of "albucid" decreased in the larger army hospitals, but since it was not available to civilians, it was still the most popular ophthalmic drug in England when I left in 1945 I have been surprised to find so little mention of this drug in the ophthalmic literature of the United States, and this report has been very timely I hope that Sir Stewart Duke-Elder will say something of the present status of this drug in England

DR OSCAR WILKINSON, Washington, D C I wish to report therapeutic results in cases of ulcer of the cornea with the use of a concentrated solution of this drug The secret of the results with this drug is the concentration of the solution Recently, I had the opportunity of treating 3 patients with dendritic ulcer They had received the ordinary remedies for three or four weeks Penicillin or an ointment containing 5 per cent sodium sulfathiazole had been used with atropine and the ordinary remedies, and 2 of the patients had protein therapy Within twenty-four hours, with the drug administered every two hours, each patient had striking relief, and within three and a half or four days the eyes were practically clear I cannot account for such rapid relief except that the drug is a very efficient remedy in this type of ulcer With some other ulcers it did not seem so effective In fact, I think it is like the other sulfonamide drugs, if there is a closed source of infection, the drug will not work so well

Recently I had a patient who had had recurrent ulcers for three or four weeks, he also had dental abscesses He immediately improved with the sulfonamide treatment after extraction of his teeth

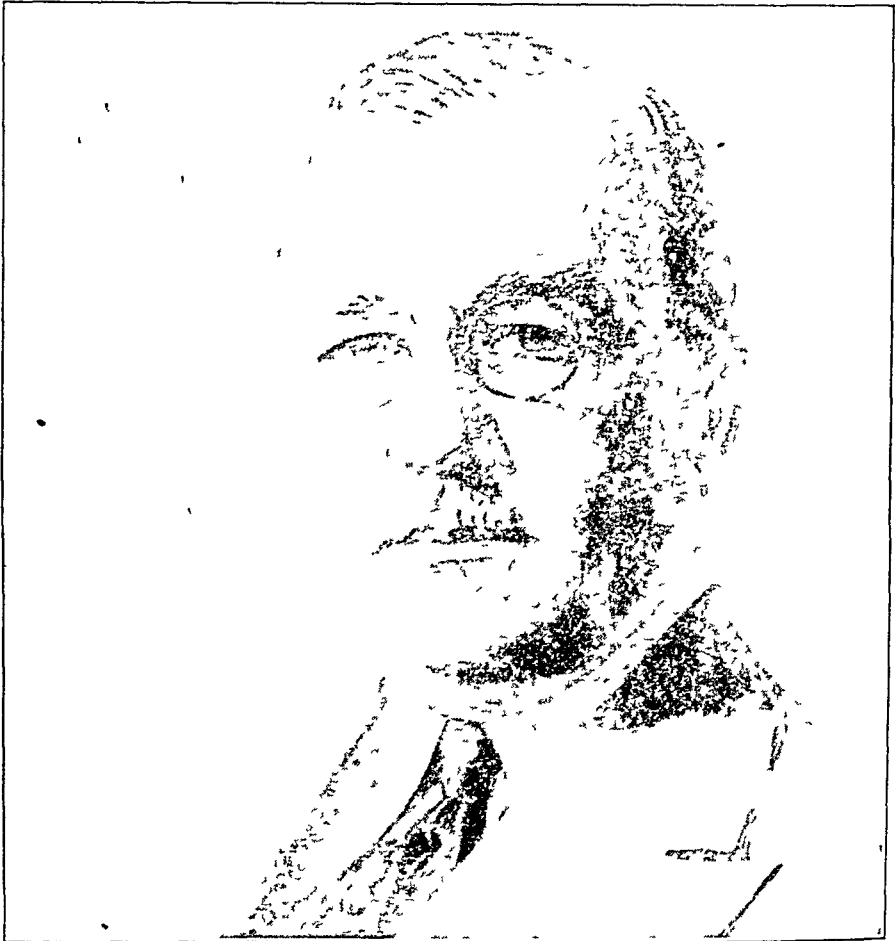
DR LEO L. MAYER, St Louis I agree with Dr Thygeson that the future use of antiseptics is a large study, but my reason for presenting this paper was the fact that the drug had been in general use for so long in Europe and had had so little mention in the literature here, and it seems to be a most efficient drug

I also agree with Dr Thygeson that there is practically no drug in use to which some one is not sensitive, I was fortunate that I had no reactions in the patients I treated I understand that Dr Hedwig Kuhn, of Hammond, Ind, also made such a report

## Obituaries

### ERVIN TOROK, M D 1877-1947

Ervin Torok died on Nov 4, 1947 at the age of 70. He had practiced ophthalmology in New York for forty years. Dr. Torok was a native of Hungary, where he graduated from the University of Budapest and received his doctor's degree in 1899. He received his preliminary education in ophthalmology in Budapest at the clinics of Grosz and Blaskovics. After several years of postgraduate training



ERVIN TOROK, M D  
1877-1947

ing at the ophthalmic hospitals of the Universities of Budapest and Berlin he arrived in the United States in 1905 with a letter of introduction to Dr. Herman Knapp and then became resident at the New York Ophthalmic and Aural Institute. He was made full surgeon in 1913, when the hospital moved uptown and its name was changed to

the Herman Knapp Memorial Eye Hospital. He resigned as surgeon in 1927, to become professor of ophthalmology at the New York Polyclinic Hospital.

In 1912 he was appointed ophthalmologist at the Beth Israel Hospital in New York city, he organized the department of ophthalmology at this rapidly growing hospital, and he remained its chief for twenty-five years, until his resignation in 1938. His other, many hospital affiliations included Beekman Street Hospital and several institutions in Westchester County. In his later years, Dr. Torok remained in active service only at the New York Polyclinic Medical School and Hospital. His interests there were equally divided among postgraduate teaching, surgery and clinical ophthalmology.

He became a member of the American Ophthalmological Society in 1912.

Dr. Torok published papers both in Hungarian and in English on various, mostly surgical, subjects, and he is the author, together with Dr. Gerald H. Grout, of "Surgery of the Eye, a Handbook for Students and Practitioners," which was published in English in 1913 and later translated into Spanish. The book describes the surgical technic of the Blaskovics clinic.

Ervin Torok's knowledge and experience in clinical, and especially surgical, ophthalmology was vast. It was a pleasure to watch the facility of his surgical skill. He was one of the first in this country to perform the scleral resection (Muller's operation) for high myopia. He also devised a method of intracapsular extraction consisting in grasping the anterior capsule with a blunt forceps and then extracting the lens by traction and by exerting pressure according to the usual von Graefe procedure.

Like so many physicians of his generation, he was a great clinician of the old school. But those who knew him well will probably remember him best for his kindness toward all his friends, his students and even the humblest of his clinic patients. During a close and almost daily association for over a dozen years, I do not remember having seen him lose his patience even once. To his very end, tragically aware of the nature of his fatal disease, he did not seem to lose interest in his patients. His concern for their welfare was equaled by their devotion to him. In those who had the privilege of being close to him, he will live on and his memory will endure.

ERNST F. LYON, M.D.

# News and Notes

EDITED BY DR W L BENEDICT

## GENERAL NEWS

**Training for Orthoptic Technicians, George Washington University School of Medicine**—The training of orthoptic technicians will be resumed by the Department of Ophthalmology of the George Washington University School of Medicine, Washington, D C, beginning April 1, 1948. The training consists of six months of didactic and practical instruction and two months of "internship." Preference will be given to students who plan to combine the teaching of other students with the administration of orthoptic procedures in their respective communities.

The course of instruction will be under the direction of Dr Ernest Sheppard, professor of ophthalmology, George Washington University School of Medicine, and Mary Everist Kramer, supervisor of the Department of Orthoptics of the George Washington University Hospital. The staff of the Department of Ophthalmology will assist with the teaching. It is anticipated that the students will have the opportunity of visiting other orthoptic clinics in the nearby vicinity during their period of internship.

Information regarding the orthoptic courses can be obtained from Dr Ernest Sheppard, 1801 K Street N W, Washington 6, D C.

**The Sanford R Gifford Memorial Lecture**—The fourth annual Sanford R Gifford Memorial Lecture was given at the Murphy Memorial Auditorium, Chicago, on Monday, Jan 26, 1948, by Dr Lawrence T Post, of St Louis. The subject of the lecture was "Practical Considerations in the Diagnosis and Treatment of Strabismus."

**American Board of Ophthalmology**—Practical examinations of the American Board of Ophthalmology for 1948 will be held at Baltimore, May 20 to 25, and at Chicago, October 6 to 9. For further information, apply to Dr S Judd Beach, Cape Cottage, Maine.

## UNIVERSITY NEWS

**Post-Graduate Course in Ophthalmology, University of Michigan Medical School**—The School of Post-Graduate Medicine of the University of Michigan Medical School announces the annual postgraduate course in ophthalmology for qualified physicians, May 6, 7 and 8, 1948, to be given at the Horace H Rackham Graduate Building, Ann Arbor, Mich., under the direction of the department of ophthalmology, University of Michigan. Complete program and details will be mailed on request to Dr Howard H Cummings, chairman of the School of Post-Graduate Medicine, University Hospital, Ann Arbor, Mich.

# Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

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## Conjunctiva

CLINICAL SIGNS OF DIAGNOSTIC IMPORTANCE IN CONJUNCTIVITIS.  
P. THYGESON. J A M A 133: 437 (Feb 15) 1947.

There are a number of clinical signs, both gross and biomicroscopic, which are of importance in the diagnosis of conjunctivitis. Changes in the regional lymph nodes, the lid margins, the limbus and the cornea are of almost equal diagnostic importance with those occurring in the conjunctiva itself. By clinical examination alone it is possible to identify many of the various etiologic types of conjunctivitis. When these clinical observations are correlated with cytologic and bacteriologic studies, the cause can be determined in a high percentage of cases.

J A M A (W ZENTMAYER)

## Cornea and Sclera

CORNEA VERTICILLATA. M GRUBER, *Ophthalmologica* 112: 88 (Aug) 1946

In a previous article (*Ophthalmologica* 111: 120, 1946) the author had reported cases of this rare corneal disease. In the second article, he describes additional cases of cornea verticillata in a second family. He believes that it is an unusual hereditary variation of physiologic character but the manner of transmission is not as yet completely known. Good illustrations of the condition are given in the paper.

F. H. ADLER

BIOLOGIC INDICATOR OF SUCCESS IN TRANSPLANTATION OF THE CORNEA:  
REPORT OF 124 CASES. V. ROSHCIN, *Vestnik oftal* 24: 47, 1946.

Roshchin performed corneal transplantations in 159 cases from 1938 to 1941. Of this series, only 124 are analyzed here, namely, the cases in which operation was performed prior to 1940, as in these cases the time of observation was sufficient for evaluation of permanent results. An increase of transparent over semitransparent transplants was noted for each successive year as a result of improvement in the operative technic. The second factor of improvement in corneal transplantation was the character of the leukoma. Of 20 cases of leukoma simplex, transparent transplants were obtained in 12, or 60 per cent, because there was a sufficient amount of normal corneal elements in the host's cornea. Of 42 cases of adherent leukoma, transparent corneas were obtained in only 16, or 38 per cent. This poor result was probably due to adhesions between the leukoma and the iris, which might produce secondary glaucoma and a proliferating membrane behind the transplant, thus minimizing the results of the transplantation. Of 62 cases



of total leukoma, transparent transplants were obtained in 11, or 17.9 per cent, the poor success being the result of dense scars, or of membranous cataract adherent to the leukoma and the absence of normal corneal elements. Patients with total leukoma have the most unfavorable prognosis, but, at the same time, they are the most deserving of operation, particularly if the leukoma is bilateral. The problem of restoring sight to patients of the last category is still to be solved.

O. SITCHEVSKA

### Experimental Pathology

TREATMENT OF LEWISITE AND OTHER ARSENICAL VESICANT LESIONS OF THE EYES OF RABBITS WITH BRITISH ANTI-LEWISITE (BAL) [2,3-DIMERCAPTOPROPANOL] I. MANN, A. PIRIE and B. D. PULLINGER, *Am J Ophth* 30 421 (April) 1947

From experiments on rabbits, Mann, Pirie and Pullinger found that 2,3-dimercaptopropanol (BAL) caused little irritation to rabbit eyes, but that if instilled within five minutes after a destructive dose of lewisite (B-chlorovinyldichloroarsine) it neutralized the effects of the latter and if its instillation was delayed up to twenty-five minutes it saved the function of the eye, although partial permanent damage remained. It was not effective against mustard gas (2-chloroethyl-sulfide) when this was used with lewisite.

W. S. REESE

### General

THE COLD PRESSOR TEST IN OPHTHALMOLOGY J. A. VAN LOON, *Ophthalmologica* 112:63 (Aug) 1946

The cold pressor test is a standard method of measuring the reaction of arterial blood pressure and was first described by Heinz and Brown (Heinz, E. A., and Brown, G. E. *Proc Staff Meet, Mayo Clin* 7 332, 1932). The procedure consists in measuring the patient's blood pressure while in the prone position during an interval of thirty minutes until the final resting value is obtained. When this has been reached, the patient plunges his hand down to the wrist for one minute in a basin with ice water, and during the immersion the blood pressure is taken every thirty to sixty seconds. The patient then withdraws the hand from the ice water, and the blood pressure is again taken, until it has returned to the previous value.

In the normal subject, the immersion of the hand into ice water causes a rise of blood pressure which is about 12 mm of mercury for systolic and 10 mm of mercury for diastolic pressure. Patients whose reaction exceeds 12 and 10 mm of mercury, respectively, are called hyperreactors. In some cases a hyperreaction amounts to a maximum of 22 mm of mercury for the systolic pressure and 18 mm of mercury for the diastolic pressure. These cases are generally found among patients with hyperthyroidism, neurocirculatory asthenia and Raynaud's disease. The present paper concerns the evaluation of the changes in blood pressure in 12 patients with spasm of the retinal arteries and 18 patients with thrombosis of the retinal veins. The author found that the patients with spasm of the retinal arteries acted as hyperreactors,

whereas the majority of patients with venous thrombosis showed no rise of blood pressure due to the cold. From this, the author concludes that the conception of venous thrombosis appearing in consequence of a temporary spasm of the supplying artery becomes highly improbable.

F. H. ADLER

### General Pathology

A CONTRIBUTION TO THE KNOWLEDGE OF OCULAR SIDEROSIS AND POSTERIOR DEGENERATIVE PANNUS. A. LOEWENSTEIN and J. FOSTER, *Am J Ophth* 30: 275 (March) 1947

Loewenstein and Foster give the findings in an eye which had retained an intraocular foreign body for twenty-two years. They found iron in Bowman's membrane, the zonular fibers, which had ruptured, the lens capsule, the retinal periphery; the choroid, and the peripheral hexagonal cells. There was a granular substance between the choroid and the retina, with a remarkable, probably vascular, network, a highly developed posterior degenerative pannus, the vascular walls of which were completely infiltrated with fat. W. S. REESE

### Glaucoma

NEW TRENDS IN STUDY OF GLAUCOMA. A. SAMOILOV, *Vestnik oftal* 24: 3, 1946

Samoilov reviews briefly the numerous theories of the pathogenesis of glaucoma. The three cardinal symptoms of prodromal glaucoma, namely, disturbance of visual function, increased intraocular tension and ophthalmoscopic changes, are, rather, manifestations of late stages of glaucoma. The only early symptom is the glaucomatous edema of the retina and the appearance as a result of the edema, of pericentral (or ring) scotomas (as demonstrated by Dashevsky). Many complaints, such as the seeing of colors of the rainbow and blurring of vision, are based on the edema of the eye. The scotoma due to the retinal edema decreases not only with calcium iontophoresis, but also with instillation of pilocarpine into the eye. On this basis Samoilov devised his campimetric pilocarpine test. Pilocarpine decreases the glaucomatous scotoma regardless of whether the intraocular tension is reduced or remains unchanged, the adaptation curve is also normalized with calcium iontophoresis. Analysis of a number of cases in which operation was performed for glaucoma shows that even though the intraocular tension remained normal in 80 to 90 per cent visual function was preserved only in from 20 to 40 per cent of the surgical cases.

The pathologic study of blindness due to glaucoma showed that the immediate cause of blindness was the destruction of the nerve elements of the retina and the optic nerve.

Thus, Samoilov concludes that the basic element in the glaucomatous process in the initial period is the retinal edema with characteristic scotomas, which decrease under the action of pilocarpine. In the later stage of glaucoma the visual fields begin to change on the nasal side and the scotomas do not disappear or decrease with instillation of pilo-

carpine Gradually, the edema is replaced with atrophy of the retinal tissue

This concept offers a broad path for study of the complexities of the eternal problem of glaucoma and its pathogenesis O SITCHEVSKA

### Injuries

OCULAR HISTOPATHOLOGY OF SOME NAGASAKI ATOMIC-BOMB CASUALTIES T F SCHLAEGEL JR. *Am J Ophth* 30: 127 (Feb) 1947

Schlaegel reports his observations on sectioned eyes of patients who died of the effects of the Nagasaki atomic bomb irradiation one month after the bombing. The histologic changes may be classified as those apparently due to direct irradiation and those due to the systemic condition. The cornea and lens may have been damaged by direct irradiation. Some of the corneas were observed to be denuded, with evidence of epithelial regeneration. The lenses might be in the early stages of developing radiational cataracts, as evinced by small vacuoles in the superficial cortex and thickening of the posterior capsule. The following changes were due apparently to the patient's systemic condition: serous exudation into and from the ciliary body, invasion of the eye by bacilli, septic choroiditis, nodular cellular infiltration of the retina, fibrin nets on the surface of the retina, and, in 1 case, a striking distention of all the ocular vessels with white cells, most of which were mononuclear.

W ZENTMAYER

### Lids

SOME METHODS OF LID REPAIR AND RECONSTRUCTION S A FOX, *Am J Ophth* 30: 190 (Feb) 1947

Fox found that by using a series of acrylic forms, socket reconstruction with epidermis, both total and subtotal, is expedited and facilitated. Use of the Padgett dermatome assures a uniformly thin graft, which is easily handled if the technic outlined is followed. The middle of the inner surface of the arm is favored as the donor site. W S REESE

### Methods of Examination

ELECTROENCEPHALOGRAPHY AND OPHTHALMOLOGY A CALLAHAN and F. C REDLICH, *Am J. Ophth* 29: 1522 (Dec) 1946

Callahan and Redlich give a brief résumé of the history of electroencephalography, some of its physiologic facts and its clinical use. The technic and its application to ophthalmology are discussed. The authors have employed it to record the galvanic response of the skin after visual stimulation and thus been able to differentiate true and false blindness. It has also aided in localizing cerebral lesions with visual defects.

W S REESE

REGARDING GONIOPHOTOGRAPHY. R R BARRIOS and R V BARRIERRE, *Am J Ophth* 30: 49 (Jan) 1947

Barrios and Barriere use Goldman's contact lens and the Haag-Streit slit lamp for goniophotography, placing a Leica camera in the

position of one of the oculars. This camera is provided with a microscopic device which permits the exact focusing of the part to be photographed. They believe that the perfection of this technic, especially with color films, will be most useful.

W S REESE.

### Neurology

THE AUTONOMIC NERVOUS SYSTEM IN OCULAR DISEASES D. O. HARRINGTON, *Am J Ophth* 29:1405 (Nov) 1946

The relations between the eye and the autonomic nervous system are reviewed, with special reference to possible effects on ocular physiology.

The autonomic stimuli are enumerated and found to be intensely active under wartime conditions of living. Special emphasis is placed on the importance and frequency of psychic trauma as a cause of autonomic instability and of the production of both physiologic, or functional, and pathologic, or organic, ocular changes.

Clinical studies have been made on autonomically unstable persons, including certain studies on the peripheral vascular system. The results have been correlated with certain physiologic dysfunctions and pathologic changes in the retina.

The clinical picture of vasoneurotic diathesis of the autonomically unstable person is described, and it is noted that the only constant factor in all cases of central angiospastic retinopathy is the autonomic instability.

The ocular manifestations of dysfunction of the autonomic nervous system reported were as follows: (a) central angiospastic retinopathy, (b) ocular changes in Raynaud's disease, (c) amaurosis fugax, (d) migraine and (e) commotio retinae. Typical cases of each condition are presented.

It is emphasized that the difference in amaurosis fugax, central angiospastic retinopathy and Raynaud's disease are of degree only.

The condition known as migraine is a cerebral vasospastic disturbance with predominant ocular symptoms.

Commotio retinae, which embraces all conditions producing retinal edema from chemical vasomotor disturbances, is a local rather than a general autonomic response.

Psychic trauma in a susceptible person can produce as profound organic changes in connection with the autonomic nervous system as extremes of temperature, anoxemia or direct physical trauma. The greatly increased wartime incidence of certain disturbances of autonomic origin can be explained in no other way.

The almost constant association of pain with these ocular lesions can best be explained as causalgia or sympathalgia.

W S REESE.

HEREDITARY NYSTAGMUS OCCURRING AS A SEX-LINKED CHARACTER RECESSIVE IN THE FEMALE C W RUCKER, *Am J Ophth* 29:1534 (Dec) 1946

Rucker found 21 cases of nystagmus in a study of six generations in a family tree of 231 members. All were males, who inherited the defect

from unaffected females In no case did a male transmit it to his son. The manner of inheritance seems not to be related to associated head movements

W S REESE

THE INFLUENCE OF BARBITURATE ON VARIOUS FORMS OF NYSTAGMUS  
M B BENDER and F. H O'BRIEN, *Am J Ophth* 29: 1541 (Dec) 1946

From their studies of intravenous injection of sodium amytal, Bender and O'Brien conclude that barbiturates in mild doses interfere with ability to control ocular movements and ocular fixation by action on the cerebral cortex, the brain stem and intermediate neuronal structures Ocular movements not involving a cortical component might be altered by barbiturate as a result of its action on the brain stem

W S REESE

MECHANISM OF MOTION SICKNESS G MORTON, A CAPRIANI and D McEACHERN, *Arch Neurol & Psychiat* 57: 58 (Jan) 1947

Motion sickness was produced in human subjects by means of a machine designed to reproduce the wayward movements of a ship at sea The authors proved that the tendency to attribute motion sickness entirely to psychogenic causes is unwarranted and against the facts They found that motion sickness can be produced in practically every one if the right type of motion and proper position of the head are used They produced it in dogs Bilateral labyrinthectomy abolished it in dogs which had previously been highly susceptible

In addition to psychologic factors, the authors investigated many different mechanisms that have been blamed for motion sickness, such as visual and kinesthetic incoordination, movement of heavy viscera, changes in blood chemistry, vascular instability, carotid sinus reflexes and labyrinthine stimulation They conclude that the most important factor in motion sickness in man is probably stimulation of the utricles by linear accelerations in the vertical plane of the head

Evidence that incoordination of visual and kinesthetic sensations plays a minor role is the fact that no amount of visual orientation can prevent sickness in susceptible people if they are exposed to the proper type of motion Attention is called to the experiment by Jasper and Fields who took moving pictures from the subject's seat in a moving swing These were shown for over thirty minutes to a group of students in a classroom No sickness was produced

S R IRVINE

### Operations

METHOD OF SUPPLYING ADEQUATE AIR TO PATIENTS DRAPED FOR EYE OPERATIONS L RICHMOND and B FRIDMAN, *U S Nav M Bull* 46 88 (Feb) 1946

Perforated rubber tubing,  $\frac{1}{2}$  inch (1.3 cm) in diameter, is fastened across the patient's chin One end of the tubing is sealed, the open end is connected with the air stream of the air pump The perforations are placed over the chin and directed toward the nose The closed end of the tube is fitted with a metal ring A strip of hemia tape extends

from this ring around the back of the neck and is tied loosely to the opposite arm of the tubing. The patient is then draped for operation in the usual manner. The force of the air current may be regulated from the machine.

BENJAMIN FRIEDMAN.

### Orbit, Eyeball and Accessory Sinuses

INVOLVEMENT OF THE ORBIT IN CHRONIC INFLAMMATION OF THE FRONTAL SINUS M C BENFORD and H BRUNNER, *Am J. Ophth* 30:297 (March) 1947

Benford and Brunner conclude that acute orbital infections of rhinogenic origin are commoner than orbital tumors of rhinogenic origin and that these tumors arise from infections of the ethmoid cells or the frontal sinus. They may be caused by granulating periostitis, herniation of the sinus mucosa or orbital invasion by nasal polypi.

W. S REESE.

(SOME OBSERVATIONS ON THE SYMPTOMATOLOGY AND DIAGNOSIS OF CASES OF PROPTOSIS H BEY, *Brit J Ophth* 31:155 (March) 1947

The causes of proptosis may be classified as those of extraorbital or intraorbital origin and disease of the bony wall of the orbital cavity. Notwithstanding various degrees of proptosis and deviations of the eyeball, diplopia is rarely complained of and only exceptionally elicited. Careful histories should be taken and systematic local and general examinations routinely made to aid in the differential diagnosis.

Distention of the orbit may result from either intraorbital or extraorbital conditions. Intraorbital, or primary, distention is consistent with the presence of an intraorbital lesion. It was the only evidence of intraorbital tumor in 16 of 21 cases of proptosis.

W. ZENTMAYER

A CASE OF ORBITAL APEX SYNDROME IN COLLATERAL PANSINUSITIS, H KJØER, *Acta ophth* 23:357, 1945

The symptoms characteristic of the fully developed syndrome may be classified as follows: (1) motor: complete external and internal ophthalmoplegia; (2) sensory: disturbances corresponding to distribution of the lacrimal, frontal and nasociliary nerves, (3) visual: disturbances resulting from optic neuritis and subsequent atrophy, and (4) exophthalmos.

The case of a man aged 59 with this symptom complex is described. Pansinusitis was regarded as the responsible etiologic factor.

O. P. PERKINS

### The Pupil

STUDIES OF THE CAUSES OF SENILE MIOSIS AND RIGIDITY OF THE PUPIL S LARSSON and G OSTERLIND, *Acta ophth* 21:1, 1944.

The histologic examination of iris tissue removed at operation for cataract in 14 cases is described. The eyes were all studied clinically prior to operation, with particular reference to the ability of the pupil to dilate.

As a result of their observations, the authors believe that there is a relation between the power of pupillary dilatation and the degree of sphincteric degeneration. Moreover, there is excellent parallelism between the presence of postoperative and degenerative vascular changes and the power of the pupil to dilate. The observations are interpreted as showing that the background of senile miosis and rigidity of the pupil is primarily sclerosis of the vessels of the iris, with subsequent degeneration of the musculature and hyaline change in the stroma of the iris.

O. P. PERKINS

### Physiology

NEW WAYS OF STUDYING INTRAOCULAR PRESSURE A DASHEVSKY,  
Vestnik oftal 24: 18, 1946

This is an extremely interesting article, but difficult to abstract. In 1939 Dashevsky worked out a new elastotonometric method for the study of intraocular tension. The elastotonometer has a prism which presses on the cornea (similar to the Fick-Livshitz tonometer); on the base of the prism are made special circles, so that when the prism is pressed on the cornea deformity of the cornea is produced in three diameters. The tonometer records in grams the amount of pressure on the cornea. A table shows the three increasing tonometric pressures in millimeters of mercury. These pressures are transferred to a nomogram, which is calculated according to Friedenwald's theory of the logarithmic relationship of pressure and replacement of volume of fluid.

This new elastotonometer makes it possible to study the basic components of ophthalmotonus—the true intraocular pressure and the coefficient of rigidity (of Friedenwald). Dashevsky named the latter component the coefficient of reactivity because the eye responds to pressure by adequate reaction—increase of pressure. The study also led to new problems in the field of disturbance of the hydrodynamic equilibrium of the eye. The retinal edema appears as a manifestation of disturbance of the permeability of the choroidal wall.

O SITCHEVSKA

### Refraction and Accommodation

ACCOMMODATIVE ASTIGMATISM J. M. O'BRIEN and R. E. BANNON,  
Am J Ophth 30: 289 (March) 1947

O'Brien and Bannon remark the difference in the amount or axis of astigmatism during accommodation. From an examination of 50 eyes with three technics, they found a consistent increase of from 8 to 10 per cent for near vision. They believe that this should be noted in the higher degrees of astigmatism.

W. S. REESE

### Retina and Optic Nerve

ADHESIVE EPISCLERAL REACTION IN THE OPERATIVE TREATMENT OF  
RETINAL DETACHMENT L. WEEKERS, Brit J Ophth 30: 715  
(Dec) 1946

The various procedures used in the operative treatment of retinal detachment aim at promoting adhesive choroiditis at the retinal tear.

On the basis of experimental and clinical observations, especially of operative results, the author expresses the belief that, in addition to adhesive choroiditis, it is necessary to create an adhesive episcleral reaction, the importance of which is paramount, for it affords particularly firm attachments which militate against relapses. An adhesive episcleral reaction takes place irrespective of the method of perforation, provided the perforation is complete. The episcleral tissue proliferates actively, progresses in depth and becomes firmly attached to the retina. The steps in the operation for retinal detachment incorporating puncture for production of adhesive episcleral reaction are described. The nonperforating diathermic electrode is applied to the sclera. The point of the diathermy needle is placed against the sclera. Slight pressure applied as soon as the current is on causes instantaneous perforation. The needle is then swiftly withdrawn without turning off the current. A galvanocautery wire is heated to a dark red color. The sclera is then lightly touched at the required spot, and the cautery wire is immediately withdrawn. Thus a small cup is formed. After an interval of a few seconds the same maneuver is repeated and the cup deepened. With two or three such applications the perforation is completed and the fluid escapes. The reasons for the several steps in the operation are given. The operation is concluded by the evacuation of the subretinal fluid.

W ZENTMAYER

SUBJECTIVE LIGHTNING STREAKS R F MOORE, *Brit J Ophth* 31: 46 (Jan) 1947

Moore returns to a reconsideration of this subject, first discussed in the *British Journal of Ophthalmology* in October 1935, as he is now able to add the personal experiences with the symptoms of three ophthalmic surgeons and he has also become a subject of the "streaks." The streaks are very bright, of momentary duration, and travel from above down. They are curved and do not exhibit the zigzag feature of lightning. While they almost always occur at the outer side of the eyes, they certainly do occur in other positions, they persist much longer in the temporal field than elsewhere. The streaks do not occur with the eyes at rest, whether movements of the head alone will elicit them he is not sure, but believes it likely that they will. Probably in most cases the condition becomes bilateral in time. No limit can be put to the period for which they may occur. There is a close relation between the occurrence of these streaks and the simultaneous development of opacities in the vitreous. Moore believes that Verhoeff's explanation of the immediate cause of the streaks is probably the correct one, he attributes them to shrinking and partial separation of the vitreous, which then impinges on the retina on movement. Moore still believes that the streaks have no sinister meaning, either at the time or, what is more important, eventually.

W ZENTMAYER

OCULAR LESIONS FOLLOWING TRITOLUENE POISONING G. AJELLO, *Ann oftal e clin ocul* 72: 17, 1945

In the case reported a woman aged 23 employed in the preparation of tritoluene compounds complained of gradual loss of vision in the



left eye Ophthalmoscopic examination of the left eye showed the presence of round and flame-shaped hemorrhages along the course of the retinal vessels, papillitis, a macular star and hemorrhages in the vitreous

G BIETTI

### Tumors

ACHROMIC MELANOMA OF THE CHOROID J P PICENA and F P ALLENDE, *An Arg de oftal* 7:39 (April-June) 1946

The authors believe this case to be of interest because of the rarity of the achromic variety of melanoma and because the histogenesis of this tumor has long been wrongly interpreted A woman aged 80 stated that vision in the right eye had been decreasing for several months and that the eye was now blind The cornea was slightly opalescent, the anterior chamber was shallow, the ocular tension measured 33 mm of mercury (Schiotz) and the media was cloudy, making ophthalmoscopic examination difficult A tumor the size of a filbert could be seen at the posterior pole of the fundus, it was grayish white and elevated the retina The eye was enucleated because of secondary glaucoma Histologic examination revealed a malignant melanoma of achromic type

M E ALVARO

### Uvea

A CASE OF BILATERAL GENUINE IRIS-ATROPHY I CYUKRÁSZ, *Brit J. Ophth* 31 176 (March) 1947

A woman aged 24, with no history other than that of intolerable headaches and poor vision of the right eye, had always been blind in the left eye Vision in the right eye was 1/3 with a —8 D sphere Intraocular pressure in each eye was 56 mm of mercury The pupil of the right eye was eccentric, directed toward 3 o'clock and roughly triangular, reaching almost to the root of the iris The pigment border below and above on the nasal side was intact The iris tissue was atrophic, the frill being present only above and below Temporarily, a defect from 8 to 11 o'clock reached the angle of the anterior chamber, between the coloboma and the pupil a strip of iris tissue 5 mm in width had no frill or pigment border In the left eye the cornea was slightly stippled The pupil was continued as a coloboma above Two holes could be seen in the region of the iris root, one at 11 and the other from 1 to 4 o'clock The iris tissue was atrophic The greater defect was divided into two parts by a stout bundle of trabeculae There was slight iridodonesis The optic disk was atrophic and showed a deep glaucomatous cup

The author concluded that the regressive function of the iris is influenced by an inhibitory factor One can imagine that if, in these embryonic mechanics, in the activity of action and reaction, the faintest disturbance arises, the balance is overturned and there develops what Riger called dysgenesis medodermalis

W ZENTMAYER

IRIDOCYCLITIS AS A LATE RESULT OF LEPTOSPIROSIS POMONA O GSELL, K REHSTEINER and F VERREY, *Ophthalmologica* 112: 320 (Dec) 1946

A case is reported of unilateral iridocyclitis with nodules of the iris occurring in a patient who had previously recovered from an infection with *Leptospira pomona* (swineherd's meningitis). After excluding the other usual causes of iridocyclitis, the authors state the belief that the iritis in this case was due to *Leptospira pomona*. They found a high titer of agglutinins to leptospirosis pomona in the aqueous humor, together with a large increase in leukocytes. In the second case, in which the patient had also recovered from leptospirosis, the iridocyclitis came on seven months after the meningitis. In the second case, also, there were lymphocytes in the aqueous and mononuclear cells, but no agglutinin could be demonstrated.

F. H. ADLER'

### Vision

PHENOMENA OF FLUCTUATION, EXTINCTION AND COMPLETION IN VISUAL PERCEPTION M B BENDER and H L TEUBER, *Arch. Neurol. & Psychiat* 55: 627 (June) 1946

In this paper a detailed investigation of the phenomena of fluctuation, extinction and completion is presented. The study was made on a series of patients with damage to the brain, and some of the determining factors, particularly the time relationships involved, were analyzed. Observations made on after-images and in tachistoscopic and perimetric examinations were compared for each patient. Various supplementary methods were applied whenever it seemed indicated.

By fluctuation the authors mean that the visual image in the affected region may fluctuate in distinctness at a varying rate or may disappear and reappear at a certain rate. By extinction they mean that during fixation at a given point the image disappears completely in any part of the field of vision after a certain period. Between extinction and fluctuation of the visual image a continuum of intermediate states may be found. These gradations may be subsumed under the term "obscuratation" (dimming) of the image. In certain cases extinction can be demonstrated only under special conditions. Objects exposed to impaired parts of the field may become invisible on simultaneous exhibition of another stimulus in a less impaired or in an intact part. Completion of images should be understood as follows. Images involving both impaired and comparatively unimpaired regions of a field of vision are "completed" under certain conditions. This takes place in spite of the fact that the image is invisible if presented to the impaired region alone. Again, several gradations are possible. Sometimes only partial continuation of figures into the defective region is encountered.

This work demonstrates that the usual perimetric measurements give an adequate picture of loss of impairment of anatomic structure but do not unequivocally define how much a patient sees. The methods employed determine, in addition, spatial and temporal factors in perceptual organization. For example, the field of vision is different as judged by the appearance of after-images or by measuring with the tachistoscope (which presents targets at varying speeds) or by com-

pletion of simple objects, such as squares, oblongs or circles, presented to the visual field, than as judged by the results of the usual perimetric and tangent screen tests. The findings indicate that the visual projection area seems to operate in an integral fashion, circumscribed lesions not necessarily producing functional loss of an "all or none" character, and that one must think beyond simple point for point correspondence in considering what the patient actually sees.

S R IRVINE

DEPTH PERCEPTION IN INDIRECT VISION J GAUS, *Ophthalmologica* 112: 1 (Oct -Nov) 1946

Using the method of diverging threads described by Monje for testing acuity of stereoscopic vision (*Ztschr f Sinnesphysiol* 69: 73, 1940), the author determined the values for depth perception in indirect vision. His results are as follows:

- 1 Stereoscopic vision is present in the paracentral parts of the retina
- 2 The angle of rotation necessary to achieve depth perception is in inverse proportion to the distance in depth of the middle thread
- 3 The upper paracentral parts of the retina possess a depth perception more acute than that of the lower parts
- 4 The acuity of depth perception of the paracentral parts of the retina is analogous to the curves of angular visual acuity

F H ADLER

AN INTRODUCTION TO THE CLINICAL STUDY OF FUSION FREQUENCY. R WEEKERS and F ROUSSEL, *Ophthalmologica* 112: 305 (Dec) 1946

An apparatus is described for measuring the fusion frequency with intermittent light stimuli. The fixation point of the patient remains fixed, while the test objects can be thrown on any part of the retina desired. In this fashion, the authors hope to compare the results of the measurements of the critical fusion frequency with changes in the visual fields. The subject is completely dark adapted, and the pupil is dilated to get rid of the variations in the fusion frequency with size of pupil. Fusion frequency is measured at fixation and in the area 30 degrees from center. The diameter of the test object varies from 3 to 7 degrees. The authors find that the normal fusion frequency varies from 36 to 46 impulses per second. Values lower than 36 impulses per second must be looked on as pathologic.

F H ADLER.

## Book Reviews

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**A Treatise on Gonioscopy.** By Manuel Uribe-Troncoso, M.D. Price, \$10 Pp 306, with 117 illustrations, 35 in color Philadelphia F A Davis Company, 1947

This first book on gonioscopy written in the English language is a welcome addition to ophthalmic literature, especially since its author is the "father" of modern gonioscopy

The subject is completely covered, beginning with chapters on the comparative anatomy of the angle of the anterior chamber in mammalia and the microscopic anatomy of the angle in man The latter contains much new material on the relations of the insertion of the root of the iris to the shape and depth of the chamber The basic chapters include also one on the comparative physiology of the angle Ida Mann has contributed a valuable chapter on the development of the angle of the anterior chamber in the human eye

After the basic chapters, Troncoso discusses the history and development of gonioscopy and the various instruments and technics both past and present The chapter on the normal angle introduces some important ideas in nomenclature The use of the term "trabeculum" is defended, since it is a term designating the tissue as an organ to distinguish it from its component trabeculae This is entirely justifiable, in spite of the fact that the manuscript editors of the ARCHIVES have in the past insisted on using the term "trabecula" to maintain the proper Latin ending of the singular of "trabeculae" Troncoso prefers the term "rudimentary pectinate ligament fibers" to the older "iris processes" However, he continues to use the term "line of Schwalbe" which is a confusing term in the reviewer's opinion

Troncoso discusses in sequence, the senile conditions, congenital anomalies, injuries, inflammatory conditions and tumors of the angle He then discusses gonioscopy in the study of the various types of glaucoma

The final chapter, entitled "Miscellaneous Diseases," discusses gonioscopy in cases of hypoplasia of the iris and cornea mesodermal dysgenesis of the iris, essential atrophy of the iris and the Kayser-Fleischer ring in Wilson's disease (hepatolenticular degeneration) Much of this material is new

Several small misinterpretations have been noted, none of which detracts from the value of this fine work On page 240 the statement is found that "capsular extoliation has been found in a great number of cases diagnosed as simple glaucoma, the incidence varying from 70 per cent to as high as 93 per cent" My own calculations from the literature varied from 6 to 89 per cent Actually the incidence is nearer the smaller figure than the larger one

On page 239 there is a reference to 11 cases of glaucoma capsularis This figure should be 37 Again, on page 269, the author states, 'According to Sugar a visible separation of the lips of the wound can

be detected in 79 per cent of the successful and 62 per cent of the unsuccessful operations." This is a misinterpretation, since the separation of the wound lips cannot be detected gonioscopically. The figures represent the number of clinically successful and unsuccessful operations.

On page 231 Troncoso mentions the occurrence of congestive glaucoma in myopic eyes with deep anterior chamber and wide angle as an argument against the shallowness of the angle being the primary cause of acute glaucoma as 'Sugar and Kronfeld have lately been inclined to believe.' The difference in opinion here is based on the use of the term 'acute glaucoma.' The two authors mentioned use the term 'acute glaucoma' only in reference to narrow angle eyes, whether congestion is or is not present. They do not deny the occurrence of acute congestive episodes in simple glaucoma or secondary glaucoma of varying causes but consider them as different in mechanism.

Unlike Busacca (*ARCH OPTH* 35 710 [June] 1946), who stated that gonioscopy is of little value in differential diagnosis of glaucoma, Troncoso sees gonioscopy in the study of glaucoma for what it is worth. He, like most other American gonioscopists, does not expect too much from gonioscopy in the diagnosis of primary glaucoma. However, in differentiating primary and secondary glaucoma gonioscopy is invaluable. It helps to differentiate between congestive attacks of acute primary glaucoma and congestive episodes of secondary glaucoma. In cases of aphakia it is the only means of determining whether the glaucoma is secondary to adhesions obstructing the angle or is a true simple glaucoma in an aphakic eye. Gonioscopy's value in diagnosis of postoperative glaucoma is exhaustively covered by Troncoso.

The illustrations in this volume are superb and are the most complete of any material on gonioscopy. The bibliography is fairly complete. The paper, printing and binding are of excellent quality. Dr. Troncoso deserves much credit for this addition to his numerous and important contributions. The book deserves a place in every ophthalmologist's library.

H. SAUL SUGAR

**Industrial Diseases of the Visual Organ.** By Stephen de Grósz, M.D., Associate Professor, University Eye Clinic, No. 1 Budapest. Pp. 96, with 7 figures. Budapest Hungary. University Press 1947.

This monograph (in the Hungarian language) is concerned with industrial ophthalmology that is with diseases due to long-standing exposure to various hazards. accidental injuries are not included.

Chapter 1 is concerned with external diseases, caused by the direct action of dust, fumes and vapors (exposure to various mineral substances, plants or animal material). Dimethyl sulfate poisoning, of which an extensive description was previously given by the author, is characterized by stippling of the cornea due to acid fission products. The problem of goggles is stressed with demonstration of the new American models.

In chapter 2 the deleterious action of radiant energy in industry is discussed, especially photophthalmia of arc welders and cinema employees. The studies of Duke-Elder, F. Law, Birch-Hirschfeld and others are mentioned. The technical aspects of the glass industry

are described for a better understanding of glassblowers' cataract, which is decreasing constantly in frequency. Electric cataract, though an industrial accident rather than a disease, is mentioned, and the barometric and thermal changes which produce pathologic changes in the eye are considered.

Chapter 3 deals with intoxication. In addition to lead poisoning, the role of carbon disulfide (in rayon factories) and the carbonyl compounds, such as methyl bromide, trichloroethylene, benzene, 2,4,6-trinitrotoluene (TNT) and trinitrophenol, are reviewed. The peripheral portion of the optic pathway is generally involved (toxic amblyopia) with central scotoma. Probably the part affected is not the nerve, but the ganglion cells of the retina at the origin of the papillomacular bundle. It is emphasized that malnutrition is an essential factor in, if not the cause of, the toxic amblyopia. Possibly a lack of thiamine results in lowering cellular respiration. This deficiency may be brought about by the toxic products themselves or a poor utilization of thiamine which they produce or by a primary hypovitaminosis associated with undernourishment. Whereas formerly lead poisoning was of primary importance, today intoxication due to organic solvents has the lead.

The pathogenic role of carbon monoxide in producing anisocoria in divers has been stressed by French authors. Blindness due to methyl alcohol was observed regularly after warfare (nonindustrial cases), the disturbance in regeneration of rhodopsin manifests itself as dysadaptation. Like other substances (quinine), methyl alcohol sensitizes the ganglion cells to ultraviolet radiation.

The chapter on infectious diseases comprises epidemic keratitis (virus), tularemia and two "modern" diseases among agricultural workers—a benign form of leptospirosis (*méningite des jeunes porchers*), causing an influenza-like ailment accompanied with iritis, during which agglutinins may be recovered from the aqueous, and brucellosis (undulant fever), which frequently produces uveitis.

The chapter on miner's nystagmus is based on British experience. The toxic theory is rejected, and preponderance of the role of faulty illumination is stressed (Verhage's adaptometric studies). Near work, problems in illumination engineering, compensation and a program for visual improvement in industrial plants (Kuhn) are the other subjects considered. The classification of Minton and the "orthorater" (United States Army) are discussed.

Bibliographic references are given at the end of each chapter. This monograph, written for ophthalmologists, should be a valuable aid in detecting and preventing industrial lesions of the eye, and should replace the section on industrial hygiene in textbooks, which is generally inadequate, or may be completely lacking.

The preface was written by Dr. Vikol, secretary of state, and Prof. G. Horay, director of the University Eye Hospital, no. 1. Previous studies of the author's on physical therapy and vitaminology are often mentioned.

S. DE GROSZ, M.D.

**The Oculorotary Muscles** By Richard G. Scobee, M.D., Price, \$8  
Pp 359, with 113 figures St. Louis C. V. Mosby Company, 1947

The author starts this book with two handicaps. He has coined a new word, "oculorotary." This would not have been too serious if he had confined it to the title, as its meaning is fairly obvious, but he has persisted in using it with annoying frequency. To me it is an awkward word, and one for which I can find little need. He then introduces a set of abbreviations for the various oculorotary motor muscles and some of their actions. Abbreviations have a definite place in records, but they should be used sparingly in a book, and then only when their acceptance is nearly universal, which is not the case here. They definitely detract from the readability of this book.

This work is a complete treatise on ocular motility and its disturbances except that all discussion of surgical technic has been omitted. The author has used many quotations, some several pages long, from past and contemporary writers. Much of this is valuable material, not readily available to the student, yet this manner of writing makes for difficult, disconnected reading. Scobee is an ardent disciple of Chavasse, yet he would have greatly increased the value of the book for the novice (for whom he professes to have written it) if he had paraphrased Chavasse's ideas in his own words. No book of this sort can bring only the original ideas of the author; he must borrow from others, and it is entirely proper that he should give credit. It makes, however, for much better continuity of thought and smoother reading if the borrowed material is expressed in the author's own words.

In many ways, Scobee has presented a fresh approach to the subject, which should be stimulating to those familiar with the older texts. I like his short, concise chapters, with frequent subheadings. He has brought in most of the newer ideas, although he may have followed Chavasse too closely to please some readers. This adherence to the teachings of Chavasse is exemplified in the surgical treatment of a paretic muscle or in which he advocates as the first procedure always doing a recession of the antagonist. This may be attractive on a theoretic basis, but practically it will lead to trouble.

The followers of Duane will be disappointed to find so little of his teaching perpetuated in this volume. That Scobee does not believe it important or worth while to measure with prisms the deviation in the six cardinal directions will be considered a serious omission by many.

I find it difficult to evaluate this book. Many parts of it are extremely elementary, with fundamental principles hammered in by constant repetitions in italics. On the other hand, many other parts are distinctly detailed and complex, such as the discussions of physiology, the innervational causes of heterophoria and testing conditions in hyperphoria—complexities which may well leave the novice confused and discouraged. Some of the definitions are overly long and involved for students, such as those for orthophoria and angle kappa. Scobee's style, to me, is provocative. He challenges many of one's favorite ideas. His positiveness and definite rules for so many things will appeal to the student, though they may raise a skeptical eyebrow among the more experienced. Particularly open to question are the close correlations that he finds between certain symptoms and the various heterophorias; I question, also, the practical value of his carefully detailed discussion of cyclophoria.

Though most readers will find a number of things with which they cannot agree, or accept simply on the author's statement, there is a great deal of valuable material in this book. It is not the clear, simple exposition of the subject that is so sorely needed, but there is much of interest and worthy of careful study.

MAYNARD WHEELER

**The Blind Preschool Child** Edited by Berthold Lowenfeld, Ph.D.  
Price \$2 Pp 148 New York American Foundation for the  
Blind Inc 1947

The book is a compilation of papers by doctors, educators and social workers read before a National Conference on the Blind Preschool Child convened under the auspices of the American Foundation for the Blind, Inc.

The topics discussed were classified under three main heads, viz., social work aspects, educational aspects and medical aspects.

The authors stressed the importance of focusing attention not on the handicap itself but on the tensions and factors that may disrupt the normal family life. Particular attention should be paid to the parental attitudes toward the blind child. The attitude of the parents may be one of oversympathy or a feeling of rejection. Considerable discussion is devoted to the psychologic pattern which is set up in the early formative years of the blind child. The psychologic pattern is greatly influenced by mother love, home influences and environment. It has been found that children in institutions, who in the first years of their lives have been deprived of warm and human mothering care and who have been denied the normal relationships of family life, develop infantile personalities. They lack the capacity to think and talk well and do not acquire the confidence required to meet the experiences of social communication and human relationships.

The proper education and training of social workers who have to deal with the preschool blind child were stressed. Individual case work with parents and methods for guidance of mothers in making adjustments to the situation were outlined, as were also training programs and projects for bringing the mothers and children and trained social workers together for conferences and discussion of the various problems that confront the mother and child. Meetings at which opportunities were afforded mothers to observe the techniques of trained attendants and teachers in handling and instructing the blind child were described.

Placing of the preschool blind in nursery schools and kindergartens with seeing children was advocated in order that the blind child, by association with seeing children, may acquire a feeling of security and independence.

The medical subjects discussed were "Early Diagnosis of Visual Defects" by Dr. Brittain F. Payne, "Hereditary Aspects of Blindness," by Dr. Robert R. Chace, "Retrolental Fibroplasia" by Dr. Merrill J. King, and "Development and Guidance of the Blind Infant," by Dr. Arnold Gesell.



The book will be particularly valuable to social workers who are interested in aiding blind children. Ophthalmologists will find it well worth reading, as it will give them a better insight into the problems that confront the parents of blind children and the difficulties that attend the education and training of the blind child of preschool age.

THOMAS H. JOHNSON

**Non-hypophysare chiasmasyndrome** M. Gil Espinosa. Bibliotheca Ophthalmologica, supplement to *Ophthalmologica*, No. 32. Pp. 60, with 15 illustrations. Basel and New York: S. Kaiger, 1946.

After a short introduction on the anatomy and physiology of the optic chiasm, the chiasmal syndrome is described and two groups of symptoms are distinguished: (1) main symptoms, which are the result of a direct lesion of the chiasm (changes in the visual field, reduction of vision and changes in the eyeground); (2) secondary symptoms, which sometimes accompany the first group, though they are not so frequent and are not the direct result of the chiasmal lesion but depend on the kind, localization and extent of the process which has caused the chiasmal syndrome (hypophysial and hypothalamic symptoms, roentgen findings; encephaloventriculoarteriographic appearances). Surgically, the lesions which produce a chiasmal syndrome may be divided into two groups: (1) lesions which are caused by direct injury to the chiasm and (2) indirect involvement of the chiasm by hydrocephalus of the third ventricle or by indirect pressure from the adjoining parts of the brain.

Eight cases are fully recorded which illustrate the more important nonhypophysial lesions: such as craniopharyngioma, craniopharyngioma and hydrocephalus, tumor of the third ventricle and infundibulum, aneurysm, solitary tubercle and meningioma.

The author states that one can now distinguish between direct and indirect chiasmal compression, as well as suprasellar and intrasellar processes with the aid of the procedures to be indicated. The perimetric examination of the field must be made with small test objects (1 to 2 mm diameter) in order to detect the presence of early chiasmal processes. The early changes in the visual fields, their intensity, outline and chronologic development are of the greatest importance for diagnosis. In addition to the clinical symptoms, stereoscopic roentgenologic studies and encephaloventriculoarteriographic examinations give valuable information. In short according to the author, it is now almost always possible to determine the localization and the extent of the pathologic process in the chiasmal region, and thereby information of the greatest importance for prognosis and treatment is obtained.

This book is an excellent and instructive monograph on a subject of importance to the neurologist, as well as to the ophthalmologist.

ARNOLD KNAPP

## EXPERIMENTAL STUDIES OF OCULAR TUBERCULOSIS

### IX Failure of Penicillin to Affect the Course of Experimental Ocular Tuberculosis

JOHN D KENNEDY, M D

ALAN C WOODS, M D

JOHN BUCKLEY, M D

MORGAN BERTHRONG, M D

AND

EARL L BURKY, M D

BALTIMORE

THERE is little in the literature concerning the effect of penicillin on *Mycobacterium tuberculosis*. Abraham, Chain and Florey,<sup>1</sup> as a result of their in vitro experiments, reported the tubercle bacillus to be insensitive to penicillin. In Woodruff and Foster's experiment,<sup>2</sup> tubercle bacilli (type and virulence unstated) were not inhibited by 1,000 units of penicillin per cubic centimeter of culture medium. They attributed the insensitivity of the tubercle bacillus to the fact that it is among the most active destroyers of penicillin. Smith and Emmart<sup>3</sup> found that neither a concentration of 3,000 units of penicillin per hundred cubic centimeters of culture medium prevented growth of a virulent human type of bacillus in vitro nor did 800 units of penicillin affect significantly the degree of tubercle development in the chorioallantoic membrane. Gerber and Gross<sup>4</sup> reported that a concentration of 1,500 units per cubic centimeter of culture medium did not inhibit a rapidly growing nonpathogenic strain of tubercle bacilli. Only two reports are available on the effect of penicillin on the disease in experimental ani-

This work was supported by a grant-in-aid from the John and Mary R. Markle Foundation.

From the Wilmer Ophthalmological Institute and the Department of Pathology of the Johns Hopkins Hospital and University.

<sup>1</sup> Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, A. B., and Florey, H. W. Further Observations on Penicillin. *Lancet* 2: 177 (Aug 16) 1941.

<sup>2</sup> Woodruff, H. B., and Foster, J. W. In Vitro Inhibition of *Mycobacteria* by Streptothricin. *Proc. Soc. Exper. Biol. & Med.* 57: 88 (Oct) 1944.

<sup>3</sup> Smith, M. I., and Emmart, E. W. The Action of Penicillium Extracts in Experimental Tuberculosis. *Pub. Health Rep.* 59: 417 (March 31) 1944.

<sup>4</sup> Gerber, I. E., and Gross, M. Inhibition of Growth of *Mycobacterium tuberculosis* by a Mold Product. *Science* 101: 616 (June 15) 1945.

mals Robinson<sup>5</sup> carried out two series of experiments, in each instance infecting mice with an avian strain of *Mycobacterium tuberculosis*. In the first experiment, the organisms were suspended in a 1.6 per cent solution of penicillin for forty-eight hours and then injected in varying doses into mice, which were killed after three or four weeks. In the second experiment, the infected mice were treated with a dose of 1,000 units of penicillin per mouse per day for three weeks. No effect on the course of the infection was noted in either experiment. The only animal experiment in which a mammalian bacillus was used is that of Smith and Emmart<sup>3</sup>. They infected guinea pigs with a human type of bacillus. There were 13 treated animals and 16 controls in their series. The treated animals were given 500 units of penicillin daily for the first four days and then 200 units daily for the next twelve days. The dose was reduced because 4 animals died of drug toxicity during the first few days of treatment. Penicillin appears to be remarkably toxic for the guinea pig (Hamre and associates<sup>6</sup>). Inadequate supplies of penicillin caused the treatment to be discontinued after only sixteen days. At the end of forty-five days the experiment was terminated. No beneficial effect of the penicillin treatment was noted.

The statement that penicillin has no effect on the tubercle bacillus or on the course of the disease has gained universal credence. The published reports of the *in vitro* tests do not indicate any degree of sensitivity under these conditions. The two experiments carried out on experimental animals are inconclusive, owing to the use of an avian strain and an unsuitable animal in one<sup>5</sup> of the experiments and of an inadequate dose over too short a period of treatment in the other<sup>3</sup>. The question is of such importance that it was thought worthy of reinvestigation with larger doses of the drug, more particularly since, with the use of a massive dose of penicillin, bacterial endocarditis and syphilis, originally thought insusceptible to the drug, are now known to respond favorably. Furthermore, the work of Harper and Blain<sup>7</sup> and of Blain and Kennedy,<sup>8</sup> in which a massive dose of penicillin prevented invasion of the damaged intestinal wall in dogs by the gram-negative flora, lent encouragement to the hope that tubercle bacilli, also rated as insensitive to penicillin, might be amenable to similar treatment.

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5 Robinson, H. J. Toxicity and Efficacy of Penicillin, *J. Pharmacol. & Exper. Therap.* **77**: 70 (Jan.) 1943.

6 Hamre, D. M., Rake, G., McKee, C. M., and MacPhillamy, H. B. The Toxicity of Penicillin as Prepared for Clinical Use, *Am. J. M. Sc.* **206**: 642 (Nov.) 1943.

7 Harper, W. H., and Blain, A., III. The Effect of Penicillin in Experimental Intestinal Obstruction. Preliminary Report on Closed Loop Studies, *Bull. Johns Hopkins Hosp.* **76**: 221 (June) 1945.

8 Blain, A., III, and Kennedy, J. D. The Effect of Penicillin in Experimental Intestinal Obstruction. Studies on Strangulated Low Ileal Obstruction, *Bull. Johns Hopkins Hosp.* **79**: 1 (July) 1946.

In the experiments here reported the rabbit eye was chosen as the site of the tuberculous lesion to be studied. The course of ocular tuberculosis resulting from inoculation of the anterior chamber of the normal rabbit eye with the human type of tubercle bacilli is well known. The resulting ocular disease in such normal rabbits lasts about three months before final perforation or healing. The animals rarely die of concurrent systemic tuberculosis. Accurate clinical observation and evaluation of the course of the disease, as well as final histologic estimation, are possible. The distribution of penicillin in the ocular tissues after systemic injection is comparable to that found in other body tissues, smaller amounts occurring in the ocular fluids. Von Sallmann and Meyer<sup>9</sup> showed that thirty minutes after the intramuscular injection of 30 mg of sodium penicillin (the equivalent of 2,000 to 3,000 Oxford units) into rabbits the aqueous contained 0.69 microgram per cubic centimeter and had moderate antibiotic action. Struble and Bellows<sup>10</sup> gave dogs one large intravenous dose (12,800 units of penicillin per kilogram of body weight) and removed the eyes at varying intervals. The penicillin content of the various ocular tissues and fluids was assayed by the Florey method. Penicillin was detected in the eyeball within fifteen minutes. At the end of one hour the concentration was between 10 and 15 units per gram in the sclera, 1.39 units per gram in the chorioretinal layer and approximately 1 unit per cubic centimeter in the aqueous. Thereafter the values declined and barely a trace of penicillin remained in the eye after three hours. Town and Hunt<sup>11</sup> found in 35 rabbits that an intramuscular dose of 7,000 units per kilogram of body weight gave a therapeutic level of penicillin in the aqueous sixty minutes after injection, the loss thereafter being gradual.

#### EXPERIMENTAL METHODS

Sixty-five normal rabbits were inoculated in the anterior chamber of the left eye with 0.2 cc of a paper filtrate of a six week old culture of a virulent human type of tubercle bacilli. The inoculum was diluted to contain an average of 12 organisms per oil immersion field. Preliminary experiments showed that this dose produced slowly progressive, satisfactory ocular tuberculosis in the normal rabbit. The eyes were examined daily for the first three days after inoculation and thereafter at weekly intervals. The intensity of the ocular tuberculosis—ciliary congestion, tubercles and infiltration of the cornea, tubercles and inflammation of the iris, opacities of the vitreous, lesions of the fundus, caseation and rupture—was evaluated on a numerical scale from  $\frac{1}{4}$  to 4 in each eye, the final figure representing widespread caseation with imminent or actual rupture of the

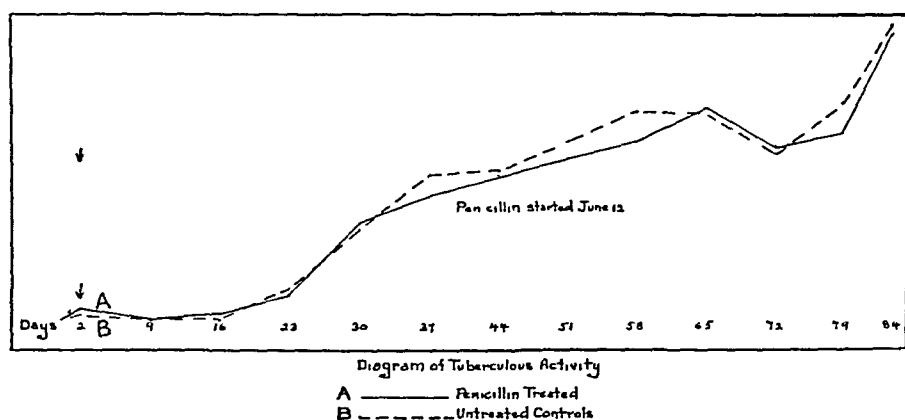
<sup>9</sup> von Sallmann, L., and Meyer, K. Penetration of Penicillin into the Eye, *Arch Ophth* **31** 1 (Jan) 1944

<sup>10</sup> Struble, G. C., and Bellows, J. G. Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, *J A M A* **125** 685 (July 8) 1944

<sup>11</sup> Town, A. E., and Hunt, M. E. Concentration of Penicillin in the Aqueous Humor Following Systemic Administration, *Am J Ophth* **29** 171 (Feb) 1946

eye Five and one-half weeks after inoculation, 32 rabbits were chosen with early, but definite, lesions, with an average rating of about 10 on the numerical scale, and were divided into two groups on the basis of equal severity. The animals in the first group, the severity of whose lesions was rated as 13 on the numerical scale, were then treated with penicillin, while the second group, with a rating of 12, were left untreated as controls.

Each treated rabbit received 200,000 units of penicillin per day<sup>12</sup>. Individual doses of 50,000 units were administered each day by subcutaneous injection at 8 a.m., 1 p.m., 7 p.m. and 12 midnight. The duration of treatment was forty-five days. On the basis of body weight this dose for a 2.5 Kg. rabbit would be the equivalent of 5,200,000 units per day for a man weighing 65 Kg. The following levels in the blood were obtained on 2 rabbits. For rabbit 69, the blood level just before injection was less than 0.025 Oxford unit per cubic centimeter, after fifteen minutes it was 8.35 units, after thirty minutes, 13.36 units, after one hour, 11.9



Tuberculous activity in the eyes of rabbits treated with penicillin (curve A) and of untreated (control) rabbits (curve B). Arrows indicate inoculation with tubercle bacilli of the anterior chamber of the left eye on May 11, 1946.

units, after two hours, 2.67 units, and after four hours 0.26 unit, per cubic centimeter. For rabbit 97, the levels for the corresponding times were 0.025 unit, 13.36 units, 12.19 units, 5.5 units, 2.0 units and 0.2 unit per cubic centimeter.

## RESULTS

*Clinical Results*—The daily treatment was maintained for a period of forty-five days. The eyes were routinely examined at least once a week, and the degree of the tuberculous lesions was evaluated. The course of the disease in the treated and in the untreated group is shown on the figure, curve A representing the course in the penicillin-treated rabbits and curve B the course in the untreated controls. As shown by the two curves, the course was practically identical in the two series, there being no clinical evidence of any inhibitory effect on the ocular

<sup>12</sup> The penicillin was supplied through the courtesy of Merck & Co., Inc., Rahway, N. J. This particular product was calcium penicillin G, containing a small amount of unknown impurities. The potency, as measured, represented penicillin G alone.

tuberculosis in the treated group. The course of the tuberculosis in these eyes was the same as that usually observed in the normal rabbit. Three rabbits of the treated group and 2 rabbits of the control group died in the course of the experiment, leaving 13 treated animals and 14 controls for evaluation of final results. At that time, of the treated animals, the eye had ruptured in 3 and was about to rupture in another. The average severity of the lesions on the numerical scale was 2.9. In the control group, 7 of the diseased eyes had ruptured, and the average severity of the lesions was 3.0. In 3 rabbits of the control series and in 1 rabbit of the penicillin-treated series the disease appeared to be healing spontaneously.

*Pathologic Observations*—The animals were killed and autopsied on the forty-fifth day of treatment. The infected eyes were removed and histologic preparations made. The lens was removed, and equatorial

*Measurements of Areas of Tuberculosis in Rabbits Treated with Penicillin and in Untreated Rabbits*

		Areas of Tuberculosis (Sq. Mm.) in Microscopic Sections						
		Clinical Activity Scale 1/4 /4	Eye			Viscera		Total Area of Tuberculosis (Eyes and Viscera)
			Non-caseous	Caseous	Total Tuberculosis for Eye	Non caseous Tuberculosis	Caseous Tuberculosis	
Group Untreated controls (14)								
Totals		41	71	63	134	9	7	150
Averages		3	5	4.5	9.5	0.6	0.5	10.6
Group Penicillin treated rabbits (13)								
Totals		37	41	30	71	11	0	82
Averages		2.9	3.2	2.3	5.5	0.8	0	6.3

sections containing all the other structures of the eye were made. No macroscopic lesions of the viscera were seen at autopsy. Sections for microscopic examination were made of the lung, liver, spleen and kidneys of each animal, in addition to those of the eye. Microscopic lesions of the viscera were observed in 6 of the treated rabbits and in 6 of the controls also.

Comparison of the degree of tuberculous involvement on a numerical basis was attempted by measuring separately the areas of non-caseous and of caseous tuberculosis, using an eyepiece fitted with a squared micrometer disk and a 32 mm objective. Doubtful lesions were checked with a 16 mm objective. There were less total ocular tuberculosis, less total ocular caseation and less total tuberculosis, both ocular and visceral, in the penicillin-treated group. There was a wide overlap, however, in the individual animals in each group. The total and average measurements for the two groups are given in the table. A statistical analysis revealed that the probability that chance alone would produce differences of such a size was just over 20 per cent. Under the conditions

of the experiment, the fact that less tuberculosis was observed in the microscopic sections from the penicillin-treated rabbits is not statistically significant. In view of the negative results, detailed figures for the individual animals are not presented.

#### COMMENT

The observations reported here require little comment. Penicillin G, given in massive doses, had no appreciable chemical effect on the course of inoculation ocular tuberculosis in the nonimmune rabbit. It likewise had no effect in preventing the spread of the organisms from the eye to the viscera, 6 animals in each series showing microscopic visceral lesions. The only possible deterrent action which could be attributed to the penicillin is the numerically lower degree of noncaseous and caseous tuberculosis in the treated group as compared with the control group. However, in each group there was a wide variation in the individual rabbits, and an analysis of these figures showed them to be without statistical significance. The conclusion that this particular sample of penicillin G had no therapeutic effect on ocular tuberculosis in the nonimmune rabbit is inescapable.

#### CONCLUSIONS

Large doses of calcium penicillin G (200,000 units per day, equivalent in amount to 5,200,000 units for a man weighing 65 Kg.) had no significant effect on experimental ocular tuberculosis in the nonimmune rabbit.

Dr. Arnold R. Rich gave valuable aid in this study, and Dr. Margaret Merrell, lecturer in preventive medicine, made the statistical analysis.

# SPASM OF MACULAR ARTERIES

Report of a Case

SIE-BOEN-LIAN, M D

BATAVIA, JAVA

IN HIS papers of 1929 and 1937, Horniker<sup>1</sup> stressed that the terminal macular vessels are easily injured by disturbances, especially of an angioneurotic (angrospastic) kind. The case of spasm of the macular arteries reported here presented a different picture from that of many macular disturbances attributed by Horniker to spasm of the terminal vessels, but the analogy is clear.

The case was one of obstruction which within a few days affected nearly all the macular arteries, including the cilioretinal artery. I had the opportunity of treating the patient for more than a year. In the beginning, I examined him daily, later, examinations were made at longer intervals. During the daily examinations of the fundus, I saw interesting changes in the affected vessels which seemed to me worthy of record.

## REPORT OF CASE

*History*—O H T, a Chinese aged 34, presented himself on Aug 25, 1944, with the complaint of blurring in his right eye the day before. Examination revealed normal visual acuity in both eyes. There were no changes in the fundus. On September 10 he consulted me again because of poor vision in the right eye for two days. After his first visit he had had a few attacks of blurred vision in the right eye, usually lasting half an hour. During the past week he had had short attacks of weakness of the left arm with cutaneous paresthesia of that arm and of the left side of the head. There was no migraine or syphilis at the time of the examination. General examination revealed a healthy appearance with no evidence of abnormality of the heart.

*Ophthalmologic Examination*—September 10. Right eye. Vision was limited to counting fingers. The cornea and media were clear. There was slight pallor of the lower half of the macular region except in an area of  $\frac{1}{2}$  disk diameter around the fovea centralis. This region is supplied by three branches of the inferior temporal artery. The pallor extended below to the second macular branch, nasally to the disk and temporally to the terminal part of the third macular branch, about 1 disk diameter to the temporal side of the fovea centralis. The last half of the second macular branch had been converted into a thin white line. The first macular branch was rather thin. The third macular branch was also somewhat narrowed and showed the following changes. Beginning just after this branch crosses the inferior temporal vein, and extending distally beyond the bifurcation for a distance of nearly 1 disk diameter, the vessel was converted

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<sup>1</sup> Horniker, E. Klin Monatsbl f Augenh 98:487, 1937



into a white column, which was sharply demarcated from the red background. Beyond this white column both vascular branches were beaded. Some of the ends of the affected artery had changed into thin white lines. The corresponding vein showed beading. There was a paracentral scotoma (fig 1).

**Left eye.** The eye was white, the cornea and media were clear. The fundus was normal. Vision was 5/4.

**Treatment.** Intravenous injections of sodium nitrite were given.

**September 11.** The changes in the inferior macular branch had disappeared. The caliber of the vessels had somewhat increased. The pallor of the lower half of the central portion of the fundus persisted. The cilioretinal artery was more contracted and appeared white for a longer distance. Edema of the upper half of the macular area caused pallor of the whole central portion of the fundus except for the foveal region. In two places the terminal portions of the small upper branches of the macular arteries looked like white lines.

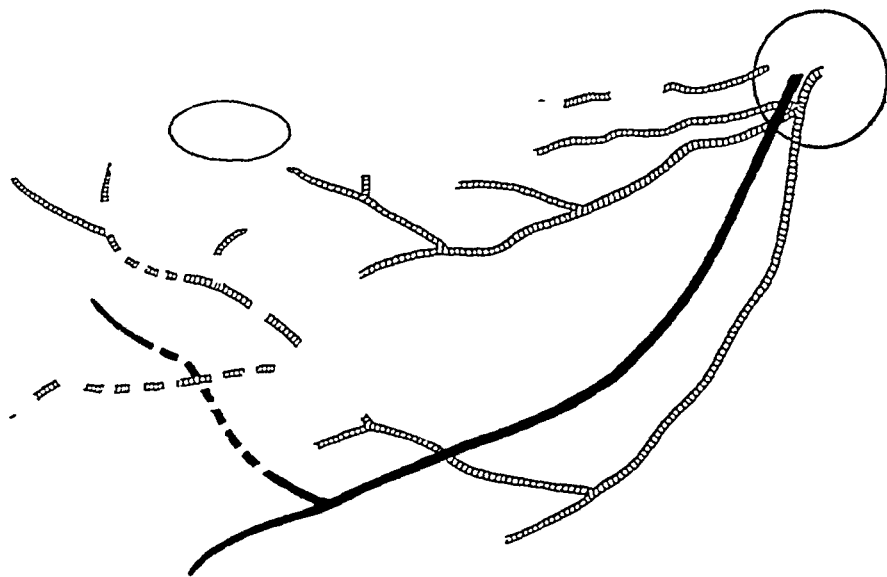


Fig 1—Spasm of the macular arteries in the right eye (Sept 10, 1944)

**September 12.** The macular vessels showed no abnormality except for the cilioretinal artery and the first inferior macular branch. Edema in the lower half of the central portion of the fundus was decreasing.

**September 14.** The terminals of the middle small branch of the superior macular artery and the distal part of the superior temporal artery were converted into white lines, with red spots in the former. There was beading of the superior macular vein, which crossed the affected artery.

**September 15.** The beading of the macular vein had completely disappeared. The affected part of the superior temporal artery showed small red segments in some places in the white column.

**September 16-27.** Daily examination of the fundus showed constant changes in the appearance of the affected area. Some of the small arterial branches, which were white formerly, had become red again or showed red particles in the white lines. On the other hand, new small vessels had become converted into white lines. The central area of the fundus, supplied by these vessels, became opaque after the vessels had become affected. Moreover, the white segment in the arteries changed constantly in size, the demarcation between the white and the red area moving

centrally or distally On September 15, just after injection of 100 mg of sodium nitrite, movement for a distance of 2 disk diameters in the direction of the disk was noted in the demarcation between the white and the red area in the peripheral part of the superior temporal artery There was no progressive movement in the affected arteries, the demarcation between the white segment and the normal red blood column of the arteries moved to and fro for a very small distance with the cardiac systole This rhythmic movement could be seen not only in the main branch but also at places far out in the periphery

When pressure was applied to the globe, the white area in the distal part of the superior temporal artery moved back centrally, but did not pass a bifurcation When the pressure was released, the white column returned to its former place, without invading the other branch of the bifurcating artery This movement of the white column with pressure on the globe did not take place at the extreme ends of the arterial branch

September 19 The affected end of the superior temporal artery proximal to the bifurcation showed an area of constriction of about 1 disk diameter, but then became almost normal in size (fig 2)

September 20 Immediately after injection of 100 mg of sodium nitrite intravenously, examination of the fundus showed a striking picture The main

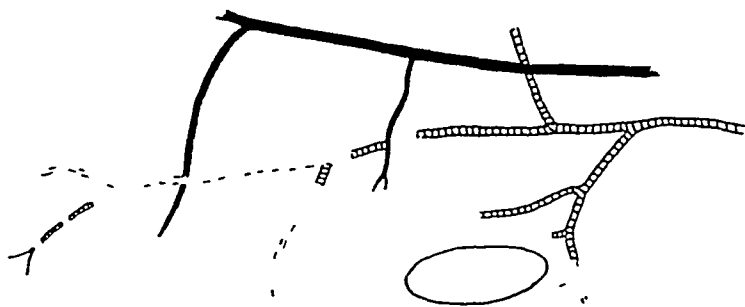


Fig 2—Constriction of the superior temporal artery (Sept 19)

superior and inferior arterial branches suddenly became pale The change from red to white extended from the periphery, progressing rapidly to the disk The caliber of the affected arteries remained normal For a few seconds there was no circulation in the two arteries except for the to and fro movement of the demarcation between the red and the white area with the cardiac systole, then a slow movement of the blood column toward the white area took place This blood column was somewhat beaded at the end With each systole it moved forward until the whole vessel became red again In addition, it was noted that the white area in the peripheral part of the superior temporal artery extended toward the disk After one-half hour the white column had not yet reached its position before the injection Vision in the right eye was 2/60

September 21 No change was apparent Up to this time no new arteries had been affected Slowly, the white part of the affected arteries became red again, and the area supplied by these vessels slowly regained its normal red color Acuity of vision in the right eye improved slowly

October 10 No new beading was to be seen, and there were no white lines at the ends of the small arterial branches Vision in the right eye was 5/30 partly The peripheral part of the superior temporal artery and the cilioretinal artery were smaller than normal The field was unchanged There was a slight opacity along the cilioretinal artery The normal foveal reflex was not noted The macular area appeared somewhat granular, with here and there white glistening spots

Feb 23, 1945 On the formerly affected parts of the retina a few glistening points could be seen

June 23, 1945 The upper macular branches were still thin Vision in the right eye was 5/30 partly

September 15 The patient was admitted to the hospital because of a tuberculous process in the apexes of both lungs

Oct. 3, 1946 There were no changes in the ocular condition, and no attacks of weakness of the arms or paresthesia had occurred

*Summary*—The case is that of a man without cardiac disease who one year after the first ocular examination presented slight tuberculous involvement of the lungs The ocular disturbance was preceded by attacks of transient blurring, weakness of the left arm and cutaneous paresthesia of the left side of the head The disturbance affected the macular region of the right eye, which was pale, first, in the lower half and, later, in the upper half The affected vessels presented the following changes Most of the terminal parts of the macular arteries and the cilioretinal artery were converted into fine white lines The peripheral parts of the branches of the inferior and superior temporal arteries showed white areas, followed by segmentation of the blood column The appearance of the macular vessels changed constantly The inferior temporal artery was normal again on the second day of examination The alteration in the superior temporal artery lasted about two weeks On one occasion, a sudden change of two arteries into white columns was noticed during an ophthalmologic examination Within a few seconds the affected vessels became normal again

#### INTERPRETATION AND ANALYSIS OF OPHTHALMOSCOPIC OBSERVATIONS ON VASCULAR CHANGES

The white lines in the terminal parts of the macular arteries undoubtedly represented spastic empty vessels The same phenomenon appeared in Grimsdale's<sup>2</sup> case of spasm of a branch of the central artery These changes cannot represent small columns of plasma, for when pressure was applied to the eyeball no movement in the demarcation between the white line and the red blood segment was observed As the white lines became red again within a shorter or longer period, they cannot represent obliterated ends of arteries The white area in the more central part of the affected arteries, I am convinced, was of the same nature as the white segments in the beaded blood column, and was also a column of plasma The phenomenon has nothing to do with embolism, in spite of the similarity of the white areas to emboli, which Coverdale<sup>3</sup> diagrammatically represented in his paper (fig 3)

The changes in the retinal artery in Benson's case of spasm of a branch of the central retinal artery have much similarity to the alteration of the arteries in my case In discussing Benson's case, Leber<sup>4</sup> suggested that the white part of the affected artery was simply a part of the vessel, filled only with plasma In the present case, the white part of the artery was not constant in size, it began at the periphery and extended to the center This fact supports the view that it was not an embolus It was also of the same nature as the white column, into which a whole main arterial branch could be changed

2 Grimsdale, H Brit J Ophth 24:208, 1940

3 Coverdale, H V Brit J Ophth 13:529, 1929

4 Leber, T, in Graefe, Á, and Saemisch, T Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1911, vol 7

The change of the two main branches of the central artery into white columns and their restoration, observed during the short period of an ophthalmoscopic examination, has, so far as I have ascertained, never before been published. It may be regarded as an accelerated development of the process of alteration in other vessels. The whole process, which usually lasts many days, took less than one minute. This observation suggests a vasomotor reaction. A change in the vessels which passes off within such a short time can have only a vasomotor origin. As there was no narrowing of the arteries, the possible spasm did not involve the central part of the vessels, but affected only the terminal parts and the capillaries. In these arteries in which the end branches were obstructed by spasm the circulation of the blood stopped. Aggregation of the red cells occurred, accounting for the presence of columns consisting only of plasma. The injection of sodium nitrite had nothing to do with the vascular change, it was only coincidental that this change took place just after the injection. After each of more than twenty injections I examined the fundus, but only twice did I see changes in the vessels. There was no circulation in the affected arteries, with each cardiac systole the demarcation between the red and the white segment moved forward a short distance, but the next moment it returned to its former place. This to and fro movement was seen far into the periphery of the arteries, indicating that the vessel was not obstructed up to that peripheral point, and that the obstruction must be looked for beyond.

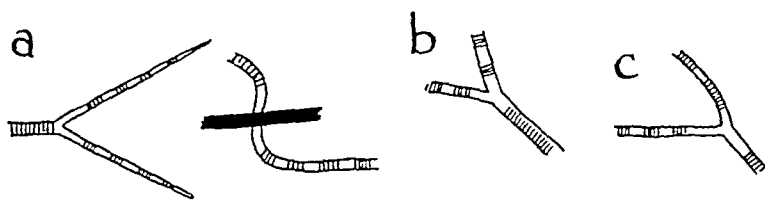


Fig 3—Segmented appearance of the central retinal artery (a) in Coverdale's case, (b) Butler's <sup>4</sup> case and (c) case presented

#### DIAGNOSIS

The clinical appearance suggests an obstruction of the macular arteries. Spasm of the arterial wall is the most probable cause of the obstruction. The diagnosis of spasm is based on the following observations: (1) prodromal obscurations of vision, (2) absence of a cardiac lesion, (3) occurrence of attacks of weakness of the arm and paresthesias, pointing to spastic narrowing of certain cerebral vessels, (4) occasional alteration in the caliber of the affected vessels and changes in the terminal arterial branches into thin white lines, and (5) simultaneous involvement of the macular branches of the central retinal artery and of the cilioretinal artery.

The appearance of the changes in the vessels in cases of retinal disturbance recorded in the literature as being due to spasm of the vessels is not wholly similar to that in the present case. Many authors observed constriction of all the arteries (Halbertsma,<sup>5</sup> Nasir Farid Bey,<sup>6</sup> Maria Rosenstein<sup>7</sup>) with normal (Nasir Farid Bey<sup>6</sup>) or contracted (Rosenstein<sup>7</sup>) veins. Halbertsma<sup>5</sup> noted beading of the veins. Hairi<sup>8</sup> saw a change of the inferior temporal artery in a white

5 Halbertsma, K. T. G. *Am d'ocul* 168 641, 1926

6 Bey, N. F. *Brit J Ophth* 14:402, 1930

7 Rosenstein, M. *Klin Monatsbl f Augenh* 75 257, 1925

8 Hairi, H. *Ann d'ocul* 158 662, 1926

line, and Harms noted such changes in all retinal arteries Kraupa and Hahn,<sup>9</sup> in a case of sudden blindness in a 5 year old child, noted edema of the retina, with normal arteries but enlarged veins, and attributed this disturbance to spasm of the capillaries This view was strongly opposed by Kubik.<sup>10</sup>

Enlargement of the retinal veins was seen by Feigenbaum<sup>11</sup> in a case of transitory blurring of vision The arteries were normal, and Feigenbaum suggested that the obscuration was due to obstruction of the venous return and that this might be caused by retrobulbar spasm of the central vein

As already noted, there is evidence that the spasm occurs in the terminal parts of the arterial branches or in the capillaries This spastic contraction may be an allergic vascular reaction In the macular region, the choroidal capillaries show the densest reticular network, contain the largest quantity of blood and have the slowest circulation These factors favor the accumulation of the antigens circulating in the blood (Behr<sup>12</sup>) Organisms of low virulence, moving from a distant focus to the macular region, may produce antibodies in this area A new mass of the micro-organisms from the focus encounters the allergic tissue, antibody and antigen come into association, with release of a toxic substance of a histamine nature, which has an angiospastic effect

In the present case the observation of a mildly tuberculous process in the lung a year after the first examination points to the existence of a latent tuberculous focus somewhere in the body at the time of onset of the ocular disease, with production of an allergic state

#### SUMMARY

A case of obstruction of the macular arteries, including the cilioretinal artery, is described The obstruction is diagnosed as spasm of the ends of the affected vessels, probably of allergic origin The allergic state is thought to be due to the tubercle bacillus

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9 Kraupa, E, and Hahn, L *Klin Monatsbl f Augenh* 66 829, 1921

10 Kubik, F *Klin Monatsbl f Augenh* 68:366, 1922

11 Feigenbaum *Klin Monatsbl f Augenh* 48:190, 1922

12 Behr, cited by Zeeman, W P C *Geneesk bl u klin en lab v. d prakt* 41 69, 1946

# PATHOGENESIS OF MYOPIA

## A New Classification

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PRIOR to von Helmholtz' epochal invention of the ophthalmoscope in 1851, little was established concerning the pathology of myopia. Kepler,<sup>1</sup> early in the seventeenth century, expressed the belief that in accommodation the retina moved closer to the lens and that myopia was a disturbance of this function. Plempius,<sup>2</sup> in 1632, first examined the myopic eye anatomically and noted the increased distance between the lens and the retina. Boerhave,<sup>3</sup> in 1708, confirmed the findings of Plempius and suggested this axial lengthening and the greater convexity of the cornea as causes of myopia. The deep anterior chamber of myopic persons misled observers of that period into believing that the cornea exhibited an abnormal convexity. Morgagni,<sup>4</sup> in 1761, also gave an anatomic demonstration of the greater length of the myopic eye. Guérin,<sup>5</sup> in 1769, first mentioned the ectasia of the posterior pole. Scarpa,<sup>5</sup> in 1801, introduced the term *staphyloma posticum* but did not associate it with myopia. In the dissection of many myopic eyes, von Arlt,<sup>8</sup> in 1854, found that elongation at the expense of the posterior wall was the usual occurrence, and he can be credited with proving the relationship between increased length of the eye and near sightedness. The increased length was still confused with other factors, however, and a thicker lens, a more convex cornea and increased coefficients of refraction of the various media were equally considered as factors in the production of myopia. Even von Graefe,<sup>6</sup> prior to the introduction of the ophthalmoscope, expressed the belief that the cause of myopia was to be discovered in the vitreous humor. Finally, Donders<sup>7</sup> demonstrated, by ophthalmometric measurements, that the

From the Institute of Ophthalmology, Columbia-Presbyterian Medical Center

1 Kepler, cited by Donders,<sup>7</sup> pp 444-446

2 Cited by Parsons,<sup>118</sup> p 908

3 Cited by Donders,<sup>7</sup> p 447

4 Morgagni, J B. *The Seats and Causes of Diseases Investigated by Anatomy*, translated from the Latin by B Alexander, London, Miller and Cadell, 1769, p 299

5 Scarpa, cited by Donders,<sup>7</sup> pp 371 and 447

6 von Graefe, A, cited by Donders,<sup>7</sup> pp 447-448

7 Donders, F C. *On the Anomalies of Accommodation and Refraction of the Eye*, translated into English by W D Moore, London, New Sydenham Society, 1864, pp 332-448

myopic cornea is as flat as, or even flatter than, the normal cornea and proved that the axial form of myopia is dependent on a lengthening of the optic axis

The ophthalmoscope proved a remarkable stimulus to the development of ophthalmology in general, and myopia shared in the general enlightenment that ensued. A host of papers were written on the subject of myopia in the years immediately following von Helmholtz' introduction of the instrument. The description of the subject, presented by Donders<sup>7</sup> in his masterpiece in 1864, constitutes an excellent resumé of the opinions generally held at that time.

Donders wrote<sup>7</sup>

The distribution of Myopia, chiefly among the cultivated ranks, points directly to its principal cause. Tension of the eyes for near objects. Respecting this fact there can be no doubt. But the explanation of it is not so evident. How then is this prolongation [of the visual axis] to be explained? Three factors may here come under observation: first, pressure of the muscles on the eyeball in strong convergence of the visual axes, second, increased pressure of the fluids, resulting from accumulation of blood in the eyes in the stooping position, third, congestive processes in the fundus oculi, which, leading to softening, even in the normal, but still more under the increased pressure of the fluids of the eye, give rise to extension of the membranes. That in increased pressure the extension occurs principally at the posterior pole, is explained by want of support from the muscles of the eye at that part.

Now in connexion with the causes mentioned, the injurious effects of fine work is, by imperfect illumination, still more increased: for thus it is rendered necessary that the work be brought closer to the eyes, and that consequently the convergence be stronger, and the tendency to stooping position of the head, particularly in reading and writing, is also increased. To this it is to be ascribed, that in schools, especially in boarding schools, where, by bad light the pupils read bad print in the evening, or write with pale ink, the foundation of Myopia is laid, which in fact, is usually developed during these years. The same causes, which give rise to Myopia, are still more favorable to its further development.

Having once occurred, the Myopia is often transmitted as predisposition to posterity, and under fresh exciting causes is developed to its higher degrees. Thus the hereditary principle accumulates in the posterity the effect of the causes repeated in every generation. In some families the Myopia therefore has attained a high degree, and the danger is greater, because, according to experience, the hereditary tendency manifests itself the more certainly, the more the myopia has already been transmitted through a number of generations, and has assumed a typical character.

A legion of papers have been written about the pathogenesis and the pathology of myopia since the publication of Donder's book, but most of them have reiterated one or another of the causes he propounded. These are five in number: (1) excessive convergence, (2) excessive accommodation, (3) heredity, (4) increased pressure of the fluids with bending the head, and (5) congestion of the coats of the eye, leading to softening and ectasia. Other factors which have

been advocated are (1) too short an optic nerve (2) congenital deficiency of the sclera, (3) disorder of growth, (4) imbalance of the extraocular muscles, (5) psychic and intellectual relation, (6) endocrine dysfunction, (7) avitaminoses, (8) constitutional diseases, (9) biologic variation and (10) sclerochoroiditis

#### ETIOLOGIC FACTORS IN MYOPIA

*Excessive Convergence*—The first theory to receive serious consideration as the cause of myopia was that of excessive convergence. Von Arlt<sup>8</sup> expressed the opinion that the pressure of the extraocular muscles in convergence impeded the outflow of blood from the eye through the vortex veins, resulting in congestion and increased intraocular tension. He regarded the external rectus and the inferior oblique muscles as the main offenders. Von Helmholtz<sup>9</sup> expressed a similar opinion, and he wrote in 1856 that looking at near objects and converging too much causes stretching, pulling and distention of the eye from increased blood pressure and muscular strain. Von Graefe,<sup>10</sup> concurring, stated the opinion that the lateral and medial rectus muscles were responsible. This led to a series of prophylactic and therapeutic tenotomies of the medial rectus muscles. Gerloff<sup>11</sup> even recommended tenotomy of both lateral and medial rectus muscles. Stilling<sup>12</sup> incriminated the superior oblique muscle and made an extensive survey of the problem. He taught that myopia varied with the position of the trochlea, if it was low, the globe was considerably compressed. He tried to prove that the orbit, and so the pulley, is low and broad in myopic persons, and he divided people into types according to the bony configuration of their orbits. Baer,<sup>13</sup> Schmidt-Rimpler,<sup>13</sup> Seggel,<sup>13</sup> Herrnheiser<sup>13</sup> and Weiss<sup>13</sup> duplicated his studies but failed to confirm his results. Müller,<sup>14</sup> believing the inferior oblique to be the cause, tenotomized this muscle in 21 patients and reported decrease in the myopia, retrogression of the chorioretinal changes and improvement in the visual acuity.

8 von Arlt, C. F. Ueber die Ursachen und die Entstehung der Kurzsichtigkeit, Vienna, Wilhelm Braumüller, 1876

9 von Helmholtz, H. Handbuch der physiologischen Optik, Ithaca, N. Y., translated and published by Optical Society of America, 1924, vol. 1, p. 141

10 von Graefe, A. Beiträge zur Physiologie und Pathologie der schiefen Augenmuskeln, Arch. f. Ophth. 1: 1-167, 1854

11 Cited by Parsons,<sup>118</sup> p. 924

12 Stilling, J. Ueber das Wachsthum der Orbita und dessen Beziehungen zur Refraction, Arch. f. Augenh. 22: 47-60, 1891

13 Cited by Parsons,<sup>118</sup> p. 925

14 Müller, L. Ueber Pathogenese und Behandlung der Kurzsichtigkeit und ihre Folgen, Wien klin. Wchnschr. 39: 321-325, 1926



Other investigators have attributed myopia to excessive convergence, omitting the factor of increased intraocular pressure. Foerster<sup>15</sup> taught that myopia and its tendency to increase were directly due to excessive convergence of the visual axes. He asserted that it could be prevented by use of full correction or with abducting prisms, and he published notes on 51 cases in which cure was effected with this method. In this country, Edward Jackson<sup>16</sup> was a staunch supporter of Foerster's theory and published a number of papers on the subject. Jackson<sup>16c</sup> wrote

Myopia's pathology begins, continues, and is most extensive at the temporal side of the optic nerve entrance. The myopic crescents and atrophies have this location. The main obstacle to free movement of the eyeball is the rigid optic nerve, firmly attached to the sclera. In convergence this resistance is constantly added to that of opposing muscles and other tissues. On the nasal side, the tissues are jammed together by the turning in of the eyeball. On the temporal, they are put on the stretch, and the choroid is pressed between the sclera and the contents of the globe. This results in the pathology seen in the myopic fundus. They are the constant and essential lesion of myopia.

He also advocated control of myopia by full correction with concave lenses or with abducting prisms. Harlan,<sup>17</sup> Lancaster,<sup>18</sup> Dvorak,<sup>19</sup> Luedde<sup>20</sup> and many others have been proponents of this theory.

*Excessive Accommodation*—The earliest proponents of accommodation as the cause of myopia stated the belief that the intraocular tension was raised during accommodation. Kepler,<sup>1</sup> Ware,<sup>21</sup> von Arlt,<sup>3</sup> Donders,<sup>7</sup> Erismann,<sup>22</sup> Dobrowolsky,<sup>11</sup> Mauthner,<sup>11</sup> Mackenzie<sup>23</sup> and Junge<sup>24</sup> expressed this belief. Hess and Heine<sup>25</sup> disproved this

15 Foerster, R. On the Influence of Concave Glasses and Convergence of the Ocular Axes in the Increase of Myopia, translated by J. A. Spaulding, *Arch Ophth* **15** 399-435, 1886.

16 Jackson, E. (a) The Full Correction of Ametropia, *Tr. Sect. Ophth., A. M. A.*, 1891, p. 133, (b) The Full Correction of Myopia, *Tr. Am. Ophth. Soc.* **6** 359-373, 1892, (c) The Control of Myopia, *Am. J. Ophth.* **14** 719-725, 1931, (d) Control of Myopia, *J. A. M. A.* **105** 1412-1416 (Nov. 2) 1935.

17 Harlan, G. C. Constant Correction of High Myopia, *Tr. Am. Ophth. Soc.* **6** 374-387, 1892.

18 Lancaster, W. B., in discussion on Jackson<sup>16d</sup>.

19 Dvorak, J. E. Present Status of the Management of Myopia, *J. Iowa M. Soc.* **26** 25-31, 1936.

20 Luedde, W. H. Monocular Cycloplegia for the Control of Myopia, *Am. J. Ophth.* **15** 603-610, 1932.

21 Ware, J. Observations Relative to the Near and Distant Sight of Different Persons, *Phil. Tr. Roy. Soc., London*, 1813, p. 31.

22 Erismann, F. Ein Beitrag zur Entwicklungs-Geschichte der Myopie, *Arch. f. Ophth.* **17** 1-56, 1871.

23 Mackenzie, W. Practical Treatise on the Diseases of the Eye, Boston, Carter, Hender & Co., 1833, pp. 593-604.

tenet by demonstrating that even maximal contraction of the ciliary muscle does not result in increased intraocular tension Duke-Elder<sup>26</sup> cited considerable evidence produced by a number of investigators to prove that accommodation and convergence have no influence on the tension clinically Moreover, accommodation is thought to assist in lowering the intraocular pressure by constricting the anterior ciliary arteries, by opening up the choroidal veins and by opening the angle of the anterior chamber Ochi<sup>27</sup> produced artificial compression of the globes in experimental animals, by increasing the compression of the extraocular muscles, in an attempt to produce axial lengthening but was unsuccessful Further, some observers have reported a connection between myopia and hypotension (Duke-Elder,<sup>28</sup> Lagrange,<sup>29</sup> Urio<sup>29</sup>)

Newman<sup>30</sup> attributed the development of myopia to the effects of excessive accommodation on the choroid He stated that accommodation pulls on the elastic membrane of the choroid, tensing it and decreasing its nutrition, so that it may give way and staphyloma of the eye result Hensen and Volkers<sup>24</sup> showed that needles passed into the choroid back of the equator move little on accommodation, and around the posterior pole not at all

The most popular of all the theories of myopia, even to the present day, has been Cohn's idea of school myopia Cohn postulated that myopia was caused by near work in school and gave as proof the fact that myopia increases in frequency and in degree during the school years He found that 14 per cent of children had myopia in the lower grades of school, a proportion that steadily rose to about 60 per cent among the university students Cohn's view had previously been expressed by Donders<sup>7</sup> It was the discovery of the incidence of myopia in schools that initiated the revolution in school hygiene It led to the insistence on clean schools, well lighted rooms, graded desks, good print, limitation of fine work, examination for ocular defects and the provision of treatment for these defects If one accepts Cohn's figures at their face value, there would seem to be no need of further occurrence of myopia, the disease should be eradicated Hogarth<sup>31</sup>

24 Cited by Parsons,<sup>118</sup> p 923

25 Hess, C, and Heine, L Arbeiten aus dem Gebiete der Akkommodationslehre, Arch f Ophth **46** 243-276, 1898

26 Duke-Elder, S Text-Book of Ophthalmology, St Louis, C V Mosby Company, 1938, vol 1, pp 518 and 522-523

27 Ochi, S Relation of the Ocular Muscles and Sclera in the Etiology of Myopia, Am J Ophth **2** 675-678, 1919

28 Duke-Elder,<sup>26</sup> 1945, vol 3, p 3418

29 Cited by Duke-Elder<sup>28</sup>

30 Newman, F A Acquired Axial Myopia, Am J Ophth **12** 714-719, 1929

31 Hogarth, M, cited by Harman,<sup>46</sup> p 11

reported that in Sweden improved hygiene, good school lighting, abolition of the old Gothic type and the increase of outdoor sports were followed by a striking reduction in the incidence of myopia

Duane<sup>32</sup> was one of the first to suggest that there is no such thing as school myopia, he was doubtful whether near work could cause near sightedness. Lawson,<sup>33</sup> who has done a good deal of work on the vision of school children, has changed his mind. In 1898 he<sup>33a</sup> expressed belief in the Cohn school of thought. In 1919 he<sup>33b</sup> refuted Cohn's hypothesis and asserted that the incidence of myopia is the same in children who do not go to school as in those who do. In an editorial in the *British Medical Journal*, he said "We now believe that myopia is neither originated nor increased by near work"<sup>33b</sup>. Thompson<sup>34</sup> reported some contradictory statistics in 1919, in a survey of myopia in different parts of England, he found a higher percentage of myopic persons in rural areas (24.2 per cent) than in urban areas (17.6 per cent). Gullstrand<sup>35</sup> denied that accommodation, convergence or near work is the cause. Parsons<sup>36</sup> stated that near work has no harmful effect on low and medium myopia. On the other hand, Duke-Elder<sup>37</sup> found that there was a larger number of cases of myopia than normal among compositors and that in a high percentage of these cases the myopia was progressive. He concluded that near work has a deleterious effect on vision and encourages the development of near sightedness. Rasmussen,<sup>38</sup> in a survey of 120,000 refractions in China, found 70 per cent of the people myopic, a figure comparable to that generally accepted in China for many centuries. He ascribes this high incidence to excessive accommodation and convergence in study, poor illumination, difficult Chinese characters and bending over low desks to read. Strangely enough, in the same article he observed that 98 per cent of the population were illiterate.

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32 Duane, A. Some Considerations on the Hygienic and Prophylactic Treatment of Myopia, New York M J 75 983-986, 1902

33 Lawson, A. (a) Abstract of a Report on the Vision of Children Attending London Elementary Schools, Brit M J 1 1614-1617, 1898, (b) School Myopia, *ibid* 2 420, 1919

34 Thompson, E. Some Statistics of Myopia in School Children, with Remarks Thereon, Brit J Ophth. 3 303-310, 1919

35 Gullstrand, A. Helmholtz Treatise of Physiologic Optics, Ithaca, N Y, Optical Society of America, 1924, vol 1, pp 379-381

36 Parsons, J. Developmental Myopia and the Treatment of Myopes, Lancet 2 796-797, 1933

37 Duke-Elder, W S. An Investigation into the Effect upon the Eyes of Occupations Involving Close Work, Brit J Ophth 14 609-620, 1930

38 Rasmussen, O D. Incidence of Myopia in China. Data and Theses from Periodical Investigations Covering Thirty Years Residence, and Association with Refracting and Hospital Centers, in a Score of the Larger Cities, Brit J Ophth 20 350-360, 1936

*Heredity*—Many ophthalmologists have expressed agreement with Donders that there is a hereditary factor in the causation of myopia. A few have affirmed that myopia is solely a hereditary disease, more have said that there is a hereditary predisposition. Duke-Elder<sup>39</sup> stated that high myopia is definitely hereditary. Gifford<sup>40</sup> wrote

The most important cause of axial myopia is hereditary, in the sense of an hereditary tendency for the eyes to reach abnormal proportions in the course of growth.

Sathaye<sup>41</sup> also claimed that heredity plays an important part in myopia, probably following the mendelian pattern. As a result of statistical studies of myopia in the east end of London among Jewish and non-Jewish children, Sourasky,<sup>42</sup> too, expressed favor toward the theory of a hereditary influence and suggested that a sex-determined factor controlled the growth of the eye. Wood<sup>43</sup> based his theory of a deficient ciliary muscle on the transmission of a hereditary defect. In a review of the subject, Prangen<sup>44</sup> wrote

In trying to arrive at the most plausible cause of myopia, heritage seems to be the one outstanding factor. Myopia is undoubtedly an inherited characteristic, which in all probability, follows Mendel's law.

Doyle<sup>45</sup> stated the opinion that the hereditary influence was questionable. Thompson<sup>45a</sup> was not able to establish any definite hereditary pattern. He found many cases of high myopia in families without any taint of near sightedness and, vice versa, many normal children of parents with a high degree of myopia. In an extensive study of 300 cases of high myopia, Harman<sup>46</sup> found a definite family history of myopia in 50 cases (17 per cent). In a later series, of 547 cases, he found such a history in 32.8 per cent. Banerjee,<sup>47</sup> studying the vision of students in India, collected 700 cases of myopia, in 40 per cent of which there was evidence of a hereditary influence.

39 Duke-Elder, W. S. *Practice of Refraction*, Philadelphia, The Blakiston Company, 1945, pp. 77-92.

40 Gifford, S. R. *Textbook of Ophthalmology*, Philadelphia, W. B. Saunders Company, 1945, pp. 52-58.

41 Sathaye, V. D. *Myopia*, Indian J. Ophth. **2**:132-138, 1941.

42 Sourasky, A. *Race, Sex, and Environment in the Development of Myopia*. Preliminary Communication, Brit. J. Ophth. **12**:197-212, 1928.

43 Wood, A. *A Suggestion as to the Cause of Myopia*, Ophthalmoscope **14**:302-306, 1916.

44 Prangen, A., deH. *The Myopia Problem*, Arch. Ophth. **22**:1083-1096 (Dec.) 1939.

45 Doyle, P. G. *The Myopic Child*, Clin. J. **52**:157, 1923.

46 Harman, N. B. *An Analysis of Three Hundred Cases of High Myopia in Children, with a Scheme for Grading Fundus Changes in Myopia*, Tr. Ophth. Soc. U. Kingdom **33**:202-220, 1913.

47 Banerjee, J. *State of Vision of Indian Students in Calcutta*, Calcutta M. J. **33**:53-63 and 285-295, 1938.

*Increased Pressure of the Intraocular Fluids on Bending the Head Forward*—Levinsohn<sup>48</sup> was the most emphatic proponent of this theory. He postulated that when the head is bent forward the eye is somewhat proptosed, owing to the action of gravity and increased congestion in the orbit. This forward displacement of the globe results in a pull on the optic nerve because all the mesodermal attachments of the eye are distensible and the nerve is not. He claimed to have proved this theory experimentally in dogs, cats, rabbits and monkeys, by suspending the animals in an inverted position for several months. Essed and Soerwarno<sup>49</sup> confirmed his observations. Marchesani<sup>50</sup> repeated Levinsohn's experiments on apes, using a control group, and found myopia as often in the controls as in the subjects. Comberg,<sup>51</sup> in measurements on corpses, observed that there is 5 mm of possible lengthening of the optic nerve, and he stated that the globe can never "hang" on the optic nerve in the sense that Levinsohn meant. Bucklers<sup>52</sup>, Scheerer and Seitzer,<sup>53</sup> and Jablonski<sup>54</sup> all repeated Levinsohn's experiments but failed to confirm his results.

Edridge-Green<sup>55</sup> favored a somewhat similar principle. He stated the belief that bending, straining and lifting increased the intraocular pressure by obstructing the flow of lymph out of the eye, and so causing distention of the sclera. Galloway<sup>56</sup> agreed with Edridge-Green and explained the incidence of myopia in laborers, farm servants and other heavy workers in this way. Lipschutz,<sup>57</sup> too, explained myopia as the result of increased intraocular pressure, due to bending the head forward.

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48 Levinsohn, G. Notes on the Genesis of Myopia, *Arch Ophth* **54** 434-439 (Sept.) 1925, Reply to Criticisms of My Theory on the Genesis of Myopia, *ibid* **15** 84-85 (Jan.) 1936.

49 Essed, W. F., and Soerwarno, M. Ueber Experimentalmyopie bei Affen, *Klin Monatsbl f Augenh* **80** 56-62, 1928.

50 Marchesani, O. Untersuchungen über die Myopiegenese (Die experimentelle Affenmyopie), *Arch f Augenh* **104** 177-191, 1931.

51 Comberg, W. Anatomic and Experimental Examinations of the Mechanical Factors in the Origin of Myopia, *Arch Ophth* **1** 286 (Feb.) 1929.

52 Bucklers, M. Anatomische Untersuchungen über die Beziehungen zwischen der senilen und der myopischen Circumpapillaren, *Arch f Ophth* **121** 243-283, 1928.

53 Scheerer, R., and Seitzer, A. Ueber das Auftreten von sogenannten myopischen Veränderungen am Augenhintergrund bei den verschiedenen Brechungszuständen des Auges, *Klin Monatsbl f Augenh* **82** 511-515, 1929.

54 Jablonski, W. Ueber den augenblicklichen Stand der Erforschung der Kurzsichtigkeit, *Zentralbl f d ges Ophth* **28** 129, 1932.

55 Edridge-Green, F. W. The Cause and Prevention of Myopia, *Lancet* **1** 136-137, 1918, Cause and Prevention of Myopia, *ibid* **1** 469-471, 1921.

56 Galloway, A. R. The Education of Myopes, *Brit M J* **2** 46, 1923.

57 Lipschutz, H. Myopia and Near Work, *Brit J Ophth* **19** 611-612, 1935.

*Congestion of the Coats, Leading to Softening*—Three men, in addition to Donders,<sup>7</sup> suggested this factor as the etiologic process. Norris<sup>58</sup> asserted that abuse of the eyes leads to congestion, infiltration of the tunics of the eye with serum and softening, so that the protective coats may give way under normal intraocular pressure. Turner<sup>59</sup> theorized that toxins from a diseased condition of the nose and throat cause chronic waterlogging of the choroid and sclera, as well as an increase in the bulk of the vitreous, and push the sclera backward without any change in the tension. Lindner<sup>60</sup> expressed the belief that in near work there is a transudation of the blood elements into the tissues about the choroidal blood vessels. This transudate causes a lowering of the resistance of the sclera by some enzymatic action. He stated the belief that the suprachoroidea serves as a protective layer for the sclera and explained the localization of myopic lesions at the posterior pole on the basis of the thinning of the suprachoroidea posteriorly. A contributing factor, Lindner suggested, is the increased transudation about the posterior pole because of the increased thickness of the choriocapillaris around the fovea.

*Too Short an Optic Nerve*—A tenet that attained some popularity about fifty years ago was the belief that the optic nerve was too short in myopic persons and so pulled on the posterior pole of the globe. This idea was first suggested by Hasner,<sup>18</sup> and the theory was fostered particularly by Weiss<sup>61</sup>. Emmert,<sup>62</sup> Paulsen<sup>63</sup> and Thorner<sup>64</sup> also advocated it. Stilling<sup>13</sup> examined and measured a series of 200 optic nerves post mortem and found the optic nerve short in very few eyes, and those few were not myopic. Schnabel,<sup>65</sup> Hess,<sup>66</sup> Comberg,<sup>51</sup> Hanssen<sup>67</sup>

58 Norris, W. F. Some Remarks on Asthenopia and the Changes in Refraction in Adolescent and Adult Eyes, *Tr. Am. Ophth. Soc.* **4** 369-384, 1886.

59 Turner, H. H. Discussion of the Elements Underlying Progressive Axial Myopia, *Pennsylvania M. J.* **34** 173-178, 1930, *The Etiology and Control of Progressive Axial Myopia*, *ibid.* **47** 793-801, 1944.

60 Lindner, K. Ueber den Einfluss von Umwelt und Vererbung auf die Entstehung der Schulmyopie, *Arch. f. Ophth.* **146** 336-376, 1946.

61 Weiss, L. Beitrage zur Entwicklung der Myopie, *Arch. f. Ophth.* **22** (pt. 3) 1-124, 1876.

62 Emmert, E. On the Causes of Myopia, *Ophthalmoscope* **2** 374-375, 1904.

63 Paulsen, O. Ueber die Entstehung des Staphyloma posticum chorioideae, *Arch. f. Ophth.* **28** 225-244, 1882.

64 Thorner, cited by Luedde<sup>20</sup>.

65 Schnabel, J. Zur Lehre von den Ursachen der Kurzsichtigkeit, *Arch. f. Ophth.* **20** (pt. 2) 1-70, 1874.

66 Hess, C. Ueber den Einfluss, den der Brechungsindex des Kammerwassers auf die Gesamt-Refraktion des Auges hat, *Klin. Monatsbl. f. Augenh.* **36** 274-280, 1898.

67 Hanssen, R. Zur Genese der Myopie, *Klin. Monatsbl. f. Augenh.* **67** 171-172, 1921.

and von Hasses<sup>68</sup> could not agree with Hasner and Weiss. In fact, von Hasses suggested that too long an optic nerve might be the cause! He observed a very long and sinuous optic nerve, resembling a spiral behind the globe, in many myopic persons, and proposed that backward movement of the globe on blinking the lids may weaken the posterior pole by causing it to hammer against this springlike optic nerve.

*Congenital Deficiency of the Sclera*—Mauthner<sup>69</sup> initiated the proposal that the staphyloma of myopia is due to congenital weakness of the sclera. This concept was then taken up by Schnabel and Herrnheiser,<sup>70</sup> who endeavored to prove it anatomically. They showed that when an emmetropic eye is placed on a flat surface with the cornea down, the eye keeps its shape. However, when a myopic eye is placed in a similar position, some part of the posterior pole will dimple inward. Luedde,<sup>70</sup> Henderson,<sup>71</sup> Dean,<sup>72</sup> Couadau<sup>73</sup> and Incze<sup>74</sup> endorsed this explanation of the pathologic basis of myopia. Incze stated that there is an asthenic tendency in myopia, in that the scleral weakness is part of a general weakness of all mesoderm-derived tissues throughout the body. According to Incze, distention of the eye results from daily fluctuating hypertonia on the weak sclera.

*Disorder of Growth*—That myopia is an overgrowth of the eyeball was proposed by Vogt<sup>75</sup> in 1923. He stated that the retina is the determinative factor in the size of the eye and that myopia results when the retina has too much inherent growth potential. He compared the growth of the eye around the retina with the growth of the skull around the brain. Stocker<sup>76</sup> endorsed Vogt's theory and attempted to explain the pathologic changes at the posterior pole on that basis.

68 von Hasses, cited by Poos, F. The Myopic Problem, *Arch Ophth* 2 66-75 (July) 1929.

69 Cited by Parsons,<sup>118</sup> p. 926.

70 Schnabel, J., and Herrnheiser, I. Ueber Staphyloma posticum, Konus und Myopie, *Ztschr f Heilk* 16 1-48, 1895, abstracted, *Jahrb u Ophth*, 1896, pp. 436-437.

71 Henderson, T. The Constitutional Factor in Myopia, *Tr Ophth Soc U Kingdom* 54 451-459, 1934.

72 Dean, F. W. Axial Myopia. Phases of Etiology and Treatment, *J Iowa M Soc* 21 216-220, 1931.

73 Couadau, A. La myopie monolaterale. Travail de la clinique ophthalmologique du Prof. Frankel, Paris, J. B. Bailliere, 1929, p. 119.

74 Incze, A. Ueber die Myopie als eine konstitutionelle Veränderung, *Ztschr f Augenh* 67 20-41, 1929.

75 Vogt, A. Ueber Vererbung von Augenleiden, *Schweiz med Wchnschr* 53 188-193, 1923.

76 Stocker, F. W. Pathologic Anatomy of the Myopic Eye with Regard to Newer Theories of Etiology and Pathogenesis of Myopia, *Arch Ophth* 30 476-488 (Oct) 1943.

According to Stocker, when the retina grows too much on the nasal aspect of the disk, supertraction ensues, and when it does not grow quite enough on the temporal side, the myopic crescent results

Holm<sup>77</sup> theorized that the tonus of the ciliary muscle is a regulating influence, directing the growth of the eye. Therefore, the increased innervation of the ciliary body required during long periods of reading acts as a growth-promoting factor, and school myopia is the common result. Progress beyond 3 D of myopia is explained by superinnervation of the ciliary muscle, the myopic student brings his book closer than his near point because convergence to that point stimulates his accommodation, and the closer he moves it, the more accommodation he needs.

Wood<sup>43</sup> held that myopia is due to lack of development of the ciliary muscle, particularly of Muller's fibers. This defect, usually described as a result of myopia, is present at birth, according to Wood, he stated, therefore, that it cannot be a phenomenon of disuse. Keith<sup>78</sup> stated the belief that it is a growth disorder, occasioned by the conditions which civilization has imposed on man. He compared myopia with acromegaly, with the idea that some comparable fault in the mechanism that regulates the growth of the sclera must be at the root of myopia. Posey<sup>79</sup> suggested that the shape of the skull determines the conformation of the orbit and, in turn, the form of the globe. Myopia, according to Posey, is common in races like the Teutons, whose skulls are long anteroposteriorly, and is rare in the Negro and the Indian, of whom the reverse is true. Vandergrift<sup>80</sup> concurred with Posey in this belief and stated that myopia is the price paid by man for his high mentality. Walker<sup>81</sup> and Duke-Elder<sup>82</sup> also expressed the opinion that axial myopia is an aberrant growth process.

*Imbalance of the Extraocular Muscles*—Marlow<sup>83</sup> observed that imbalance of the extraocular muscles is present in a high percentage of myopic eyes and suggested that this is an important, probably the most important, active factor in the onset and progress of this condition.

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<sup>77</sup> Holm, E. The Pathogenesis of Reading Myopia, *Acta ophth* **3**:234-244, 1926

<sup>78</sup> Keith, A. Myopia, a Disorder of Growth, *Lancet* **1** 32-33, 1925, On the Nature of Man's Structural Imperfections, *ibid* **2** 1047-1051, 1925

<sup>79</sup> Posey, W. C. Hygiene of the Eye, Philadelphia, J. B. Lippincott Company, 1918, p. 32

<sup>80</sup> Vandergrift, G. W. The Development of the Accommodative Apparatus in Relation to Myopia and Presbyopia, *New York State J. Med* **24** 385-389, 1924

<sup>81</sup> Walker, J. P. Myopia and Pseudo-Myopia, *Brit. J. Ophth* **30** 735-742, 1946

<sup>82</sup> Duke-Elder,<sup>39</sup> p. 79

<sup>83</sup> Marlow, F. W. Muscle Imbalance in Myopia, *Arch. Ophth* **13** 584-597 (April) 1935



He advised that an occlusion test for latent muscular imbalance be carried out in all cases as early as possible. Pascal<sup>84</sup> agreed that exophoria may produce myopia by compression of the extraocular muscles, and also by excessive stimulation of accommodation due to overstimulation of convergence. In a statistical study of functional muscle tests in axial myopia, Snell,<sup>85</sup> however, found nearly twice as much esophoria as exophoria. In his series of 1,078 cases of myopia, esophoria was exhibited in 55.3 per cent and exophoria in only 30.4 per cent. He concluded that convergence insufficiency is not a specific characteristic of myopia. In a survey of 790 cases of myopia, Thompson<sup>84</sup> found divergent squint in 29 cases (3.67 per cent) and convergent deviations in 45 cases (5.69 per cent).

*Psychic and Intellectual Relations*—Straub<sup>86</sup> maintained that the psyche is responsible for the state of refraction. Only those who wish to see well at a distance are emmetropic, and those who are overly attracted to near objects become myopic. Druault-Tonfesco<sup>87</sup> regarded a person's refraction as part of his personality and mental makeup. He claimed that myopic and hypermetropic persons do not reason, write, work or draw in the same way as emmetropic persons and that one's refraction can be determined by the style of one's writing or painting. Mills,<sup>88</sup> calling attention to the high incidence of myopia among the world's great painters, and also in a private series of artists in his own practice, asserted that there is a connection between the education and myopia. He found a close relation between near sightedness and high mental speed, intense aspiration and the severe competition of civilization. Heinonen<sup>89</sup> also found myopia bound up with the intellectual endowment.

*Endocrine Dysfunction*—Among the more modern explanations of myopia, that of an endocrine disturbance has been approved by several authors. Wiener,<sup>90</sup> in the United States, has been the strongest advocate

84 Pascal, J. I. Myopia and Exophoria, *Arch Ophth* **14** 624-626, (Oct) 1935

85 Snell, A. A Statistical Study of Functional Muscle Tests in Axial Myopia. *Tr Sect Ophth, A. M. A.*, 1936, pp 49-64

86 Straub, M. La part de l'hérédité et de l'étude dans le développement de la myopie, *Arch d'opht.* **36** 68-70, 1919

87 Druault-Tonfesco, S. Notes sur la myopie, *Ann d'ocul* **159** 709-729 and 865-888, 1922

88 Mills, L. Peripheral Vision in Art, *Arch Ophth* **16** 208-219 (Aug) 1936

89 Heinonen, O. Entsteht die Schul- und Berufsmyopie infolge der Näharbeit, oder gibt es andere Faktoren, welche sich an erster Stelle hierbei geltend machen? *Acta ophth* **6** 238-250, 1928

90 Wiener, M. Epinephrine in Progressive Myopia, *J. A. M. A.* **89** 594-596 (Aug 20) 1927, The Use of Epinephrine in Progressive Myopia. Further Report, *Ann J Ophth* **14** 520-522, 1931, Myopia Cause, Progress and Treatment, *South M J* **24** 529-534, 1931

of this hypothesis and has actively sponsored instillation of epinephrine in the eyes as a mode of therapy. In 1931 he reported results of this type of treatment in a series of 99 cases of actively progressive myopia. In 79 cases there was no further increase in refractive error after one year, while in 20 the myopia was still progressive. Wiener described the case of an intelligent woman who, when she notices her distant vision failing, instills more epinephrine drops and can see better in a very short time. Nicolato<sup>91</sup> also expressed the opinion that endocrine disturbance, especially a thymic dysfunction, is the hereditary cause of all myopia. Malone<sup>92</sup> favored an endocrine upset as the cause but did not state which gland was involved; he also reported beneficial results from epinephrine. Haseltine<sup>93</sup> expressed the opinion that progressive myopia and glaucoma are both the result of an endocrine disturbance, and reported 5 cases in which progressive myopia was definitely improved by administration of a preparation of the adrenal gland. Costello<sup>94</sup> described a syndrome of hypothyroidism and myopia. Bothman<sup>95</sup> also suggested that hypothyroidism may be a cause of myopia. He found a low basal metabolic rate in a series of cases of progressive myopia and reported that in some cases the condition ceased to progress after thyroid was given. Law<sup>96</sup> reported favorable effects from calcium and parathyroid therapy.

*Avitaminoses*—Lack of essential vitamins as a causative factor in myopia has had its adherents. Knapp<sup>97</sup> proposed that a disturbance in vitamin D-calcium-phosphorus metabolism was the cause of myopia. He suggested that lack of calcium may weaken the fibrous tunics of the eye. He reported beneficial optical results from vitamin D therapy, with some resolution of the pathologic process in the fundus and shrinkage of the globe. Laval<sup>98</sup> was not able to see any improvement in clinical

91 Nicolato, A. Della genesi della myopia. Note preventiva, Arch di ottal 36 453-468, 1929

92 Malone, J. Y. Progressive Myopia, Keratoconus, and Keratoglobus, Tr Sect Ophth, A. M. A., 1939, pp 44-52

93 Haseltine, S. L. Suprarenal Gland in the Treatment of Glaucoma, Progressive Myopia, and Some Allergic Conditions, J. M. Soc. New Jersey 34: 729-731, 1937

94 Costello, J. P. Obesity and Ocular Symptoms in Mentally Alert Children Due to Hypothyroidism, Endocrinology 20 105-106, 1936

95 Bothman, L. The Relation of Basal Metabolic Rate to Progressive Axial Myopia. Preliminary Report, Am J Ophth 14:918-924, 1931

96 Law, F. W. Calcium and Parathyroid Therapy in Progressive Myopia, Tr Ophth Soc U Kingdom 54:281-290, 1934

97 Knapp, A. A. Vitamin-D Complex in Progressive Myopia. Etiology, Pathology and Treatment, Am J Ophth 22:1329-1337, 1939

98 Laval, J. Vitamin D and Myopia, Arch Ophth 19:47-53 (Jan) 1938, The Relationship Between Myopia and Avitaminosis, Am J Ophth 24:408-412, 1941

trials with vitamin D and concluded that there is no proof that avitaminosis causes myopia. Sathaye<sup>41</sup> agreed with Knapp and advised calcium and vitamin D therapy.

*Constitutional Diseases*—Inevitably, syphilis and tuberculosis must be mentioned in any discussion of the pathogenesis of a disease. Kassas<sup>99</sup> indicted syphilis, tuberculosis and measles as predisposing factors in the causation of myopia. The inciting factor, in his opinion, is solely a poor hygienic condition. Sonder<sup>100</sup> stated the belief that the diseases of childhood are the causes of near sightedness. He based his opinion on his series of 100 cases of progressive myopia, in which every child had had one or more of the diseases of childhood. Myopia is a stigma of constitutional weakness, according to Henderson<sup>71</sup>, he suggested the phrase "scleral rickets" and said that therapy should be general, directed toward improving the constitution of the patient. In Morse's opinion,<sup>101</sup> rickets, chronic tonsillitis, intestinal disturbances, endocrine dysfunction and toxic colitis may all produce myopia. Miller<sup>102</sup> concluded that myopia is largely due to a dietary deficiency in fats. Walker<sup>103</sup> suggested that it is due to a calcium deficiency. The devitalizing effect of a neighboring infection of the nasal sinuses is the etiologic agent, in the opinion of Lemere<sup>104</sup>. Rosenow,<sup>105</sup> in a series of experiments on animals, proved that lesions in the eye may be due to absorption of toxins in the blood from a focus of infection elsewhere in the body. Nordgren<sup>106</sup> expressed the opinion that in Sweden there is a striking resemblance between general hygiene and health and the frequency of myopia.

*Biologic Variation*—All the authors cited up to this point have accepted the axial elongation of the eye, as expressed by Donders, as

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99 Kassas, J. Ueber Veranderung der Refraction bei 90 Zoglingen des Brester Knabengymnasiums in 5 Jahren, *West Ophth* **30** 829, 1914, abstracted, *Klin Monatsbl f Augenh* **17** 754, 1914.

100 Sonder. De l'influence des maladies infantiles dans l'evolution de la myopie progressive, *Arch d'opht* **37** 290-298, 1920.

101 Morse, S. Myopia as a Disease That May Be Preventable, *Am Med* **34** 115-121, 1928.

102 Miller, H. Is Myopia a Deficiency Disease? *Am J Ophth* **23** 296-305, 1940.

103 Walker, J. P. S. Progressive Myopia. A Suggestion Explaining Its Causation, and Its Treatment, *Brit J Ophth* **16** 485-488, 1932.

104 Lemere, H. B. Contributing Factors in the Etiology of Myopia. Preliminary Report, *Tr Am Acad Ophth*, 1923, pp 132-145.

105 Rosenow, E. C. Focal Infection and Elective Localization in the Pathogenesis of Diseases of the Eye, *Am J Otol, Rhin & Laryng* **36** 883-895, 1927.

106 Cited by Sorsby, A. *Modern Trends in Ophthalmology*, London, Butterworth & Company, Ltd, 1940, pp 256-267.

the pathologic basis of myopia. In 1913 Steiger<sup>107</sup> published his theory, which contradicted this whole conception of myopia, including not only the theories of its pathogenesis, but also the previously accepted view on the very architecture of the myopic eye. He proposed the unity of all the refractive errors. To Steiger, myopia was only a biologic variation. He plotted all refractive errors as physiologic variations on a binomial curve of frequency, constructed around a mean. He asserted that myopia is merely the antithesis of hypermetropia and that people are myopic or hypermetropic by the same chance variations as people are short or tall. Steiger proposed that the curvature of the cornea (which he found to vary) and the axial length of the eye are separate, independent, freely variable components of the total refraction, that these are hereditary components and that the chance association of these free variables will produce the whole range of refractive errors. This theory was a radical departure from the orthodox school of physiologic optics. In support of this view is the fact that an axial length which will produce emmetropia with a cornea within the normal range of refractive ability will produce ametropia, either hypermetropia or myopia, with another cornea of different refractive power, but still within normal range. Later it was demonstrated by Tron<sup>108</sup> that the same axial distance might be a factor in a refraction ranging from  $+6$  to  $-9$  D. Steiger's original hypothesis of the binomial curve breaks down on two main points: (1) the excess of emmetropic persons over the theoretic calculated number and (2) the excess of myopic persons over the estimated figure.

Tron carried on Steiger's work in great detail and contributed some important pieces to the puzzle. He estimated the range of refractive power of the cornea as between 37.0 and 48.1 D and gave a range for the refraction of the lens as between 20.1 and 34.0 D, an important factor which Steiger overlooked. He showed, moreover, that Steiger's curve holds true for myopia if eyes with a myopia of over 6 D or eyes showing pathologic changes in the fundus are not considered. His work also showed that axial length is a factor of great importance in cases of high myopia but is practically insignificant in cases of myopia of medium and low degrees.

Steiger's and Tron's work brought out the important conclusion that low and medium errors of refraction may well be regarded as biologic variations, and not as pathologic entities. An outstanding

107 Steiger, A. *Die Entstehung der sphärischen Refraktionen des menschlichen Auges*, Berlin, S. Karger, 1913.

108 Tron, E. *Variationsstatistische Untersuchungen über Refraktion*, *Arch f. Ophth.* **122** 1-33, 1929, *Ueber die optischen Grundlagen der Ametropie*, *ibid* **132** 182-223, 1934.

result of their work was the new idea of classifying myopia as biologic and pathologic forms

Parsons,<sup>36</sup> in 1933, expressed views that were similar to those of Steiger and Tron. He said too much significance had been attached to the length of the myopic eye and pointed out the figures given as a normal variation for the emmetropic globe. He described myopia statistically in terms of frequency variations and said that the low degrees of myopia were as normal as short stature.

Sorsby<sup>109</sup> also attacked the axial theory of myopia and considered the theory of biologic variation. He pointed out that the length of the globe was significant only with high hypermetropia and with high myopia of 6 D or more. He expressed agreement with the belief that the low and medium errors of refraction are probably physiologic variations. But while he agreed that myopia is likely to occur as a hereditary biologic variable, he still pondered the problem of use and abuse of eyes as a causative factor.

*Sclerоchoroiditis*—When von Graefe<sup>110</sup> first began to study the fundus of myopic eyes with the new ophthalmoscope, he concluded that the pathologic changes he observed in the choroid and sclera at the posterior pole were the cause of the distention of the eyes. He named the process "scleroticоchoroiditis posterior." As soon as the opportunity presented, he searched microscopically for evidence of previous inflammation in the fundus, but in vain. Donders and others of that period disagreed with him, and later he discarded this view. That myopia might be due to a disease process was, however, accepted by several other ophthalmologists of the nineteenth century, among them Knies,<sup>111</sup> Tscherning,<sup>112</sup> Nordenson,<sup>69</sup> Ferri,<sup>113</sup> Smith,<sup>114</sup> Batten<sup>115</sup> and Risley<sup>116</sup>. Tscherning divided myopia into a benign and a malignant form, the benign he held to be congenital, the malignant (over 9 D), to be due to insidious choroiditis. Ferri attributed the rapidly developing myopia

109 Sorsby, A. The Control of School Myopia, *Brit M J* 2 730-733, 1933, The Pre-Myopic State. Its Bearing on the Incidence of Myopia, *Tr Ophth Soc U Kingdom* 54 459-465, 1934.

110 von Graefe, A. Zwei Sektionsbefunde bei Scleroticо-Choroiditis posterior und Bemerkungen über diese Krankheit, *Arch f Ophth* 1(pt 1) 390-401, 1854.

111 Knies, M. Ueber Myopie und ihre Behandlung, *Arch f Ophth* 32 (pt. 3) 15-72, 1886.

112 Tscherning, M. Studien über die Aetologie der Myopie, *Arch f Ophth* 29(pt 1) 201-272, 1883.

113 Ferri, cited by Parsons,<sup>118</sup> p 927.

114 Smith, Priestley. Introduction to a Discussion on the Diagnosis, Prognosis, and Treatment of Pernicious Myopia, *Ophth Rev* 20 331-339, 1901.

115 Batten, R. D. Myopia the Result of Constitutional Disease, *Ophth Rev* 11 1-24, 1892.

116 Risley, S. D., in discussion on Harlan,<sup>17</sup> pp 383-384.

he found in previously emmetropic adults to slow choroiditis Priestley Smith strongly asserted the opinion that choroiditis, especially the syphilitic type, may give rise to rapid and pernicious myopia Risley<sup>117</sup> expressed the opinion that the stretching of the globe is due to the choroiditis and recorded as proof 9 cases of hypermetropia he had observed passing over into myopia Batten asserted that the typical crescent, also found in emmetropic and hypermetropic eyes, would seem to indicate that the myopic crescent is a form of choroiditis, and not the result of myopia In 1892 he wrote<sup>118</sup>

Why, when in addition to choroiditis and vitreous changes, there is elongation of the eye, it should be held that the dilatation is the cause of the other two, it would be hard to say I contend that it is a more warrantable assumption that myopia is caused by choroiditis, than that choroiditis is caused by myopia

Parsons,<sup>119</sup> in his textbook of pathology, wrote

It must be remembered that there is little or no difference between the ultimate effects of an inflammatory lesion and the conditions found in myopia, and that a very slight chronic inflammation may present few objective microscopical features It may be that the lower grades of myopia are entirely congenital in origin, whilst the higher grades of so-called progressive myopia have in addition etiologically a true inflammatory factor

In 1916, Koster<sup>120</sup> ascribed advanced myopia to a primary chronic infectious chorioretinitis, aggravated by prolonged near reading He said that full correction of such myopia is a blunder, it forces the patient to use his accommodation, and any exercise of the eye is deleterious, in the face of active choroiditis He advised treating the choroiditis by the usual methods De Schweinitz<sup>120</sup> also observed that myopia may result from choroiditis, usually after an acute illness

Sourasky,<sup>121</sup> who has written several illuminating papers on myopia, discussed in 1928 the presence of typical myopic crescents in cases of low hypermetropia and in cases of low myopia He stated the belief that if the crescent is to be regarded as really due to stretching these cases represent a rapid reduction of hypermetropia from a high degree to a low degree, or even to a low myopia, in other words, as manifes-

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117 Risley, S D Hypermetropic Refraction Passing While Under Observation into Myopia, *Tr Am Ophth Soc* **4** 520-531, 1887

118 Parsons, J H The Pathology of the Eye, New York, G P Putnam's Sons, 1906, vol 3, pp 908-931

119 Koster, W School Myopia, *Nederl tijdschr v geneesk* **1** 2329, 1916, abstracted, *J A M A* **67** 475-476 (Aug 5) 1916, Progressive Myopia and Its Treatment, *Nederl tijdschr v geneesk* **2** 17, 1916, abstracted, *J A M A* **67** 549 (Aug 12) 1916

120 de Schweinitz, G Diseases of the Eye, Philadelphia, W B Saunders Company, 1916, pp 127-137

121 Sourasky, A The Growth of the Eye and the Development of Myopia A Study in the Changes of Refraction During the School Period, *Brit. J Ophth* **12** 625-644, 1928

tations of this process in hypermetropic eyes According to Sourasky, then, the extensive pathologic changes sometimes found in the eyes of patients with low degrees of myopia represent stretching of a considerable degree in originally hypermetropic eyes He mentioned the changes in the vitreous frequently associated with myopia and suggested that they point to a chronic inflammatory condition of the eye Sourasky stated that he would like to say

A myopic eye elongates not because it is myopic, but because it is due to some affection Myopia, per se, is no more the cause of the progressive elongation of the globe, than a glaucomatous cup is the cause of increasing tension

In 1928, Dimitry<sup>122</sup> recalled and concurred in von Graefe's original proposition, namely, that myopia is the result of sclerochoroiditis in the posterior pole of the eye Hallett,<sup>123</sup> in 1931, made the same affirmation and offered disease of the nasal sinuses as the original focus of infection He cited Rosenow's work<sup>105</sup> demonstrating that ocular disease may be due to absorption of toxins from the blood stream Finally, Cowan,<sup>124</sup> in 1941, emphatically called attention to the necessity of differentiating refractive myopia from the myopia associated with pathologic changes in the fundus If a patient with choroiditis is hypermetropic, the state of the refraction is disregarded, according to Cowan, but if the patient is myopic, a diagnosis of myopia is made A review of the pathologic changes in the fundus associated with this condition is in order

#### PATHOLOGIC CHANGES ASSOCIATED WITH MYOPIA

A detailed study of the lesions in myopic eyes is not within the province of this paper Since "sclerochoroiditis" is one of the commonest pathologic states seen by the ophthalmologist, its pathologic features should be well known to every one It is more pertinent, then, to mention briefly the changes observed and discuss their significance

Macroscopically, the striking feature presented by a globe with myopia is axial elongation Wolff<sup>125</sup> reported a case in which the eye measured 54 mm from cornea to posterior pole Heine<sup>126</sup> demonstrated that the pathologic process causing this lengthening lies in the posterior pole of the globe This distention of the posterior pole, called staphyloma verum by von Graefe, may be a generalized process involving the whole posterior portion of the eye, with no delineation of its borders, or, more commonly, it may be limited to a definite ectasia, usually con-

122 Dimitry, T J Myopia Is Essentially a Pathological Condition, New Orleans M & S J **81** 432-436, 1928

123 Hallett, De W The Prevention of Myopia, Am J Ophth **14** 143-146, 1931

124 Cowan, A Myopia, Tr Am Acad Ophth (1941) **46** 197-205, 1942

125 Wolff, E Pathology of the Eye, Philadelphia, P Blakiston's Sons & Co, 1935, p 258

126 Heine, L Beiträge zur Anatomie des myopischen Auges, Arch f Ophth **38** 277-290, 1899

centric with the disk The presence of staphyloma is not constant, extensive pathologic changes in the fundus are also seen in eyes with an axial length well within normal limits

Grossly, section of a myopic eye will also usually show an atrophic, thin ciliary muscle, due to underdevelopment or complete lack of Muller's circular fibers As a result, the ciliary processes are less prominent and are displaced somewhat posteriorly As another consequence, the root of the iris is situated farther back than usual, and therefore the anterior chamber appears deeper in myopic persons

Ophthalmoscopically, the commonest finding in the fundus is the so-called myopic crescent This crescent (of distraction) is usually temporal to the papilla but may occur anywhere around the disk It may surround the disk, forming what is more properly called a conus Just as the retina and choroid seem pulled away from the disk temporally, they are often found pulled over on top of the disk nasally, forming the crescent of supertraction This is not commonly seen, for it is usually composed of all the layers of the retina and choroid, and so is indistinguishable from the surrounding fundus Real and apparent distortion of the disk are often observed Real distortion of the disk results from oblique insertion of the nerve, from traction of different nerve bundles as the globe distends and from crescents of supertraction Apparent distortion occurs because the point of greatest elongation is the posterior pole, with consequent backward displacement of the temporal side of the disk Through the ophthalmoscope, then, the nasal edge of the disk is closer to the observer than the temporal, and the papilla appears oblique

Nearly as common as the crescent is the choroidal atrophy seen at the posterior pole This usually begins about the disk and the fovea and, as the process becomes severer and more extensive, these two areas often fuse, forming a large centrocecal patch This process may go on to complete degeneration of the choroid, so that the nearly bare sclera shines through As in other forms of choroiditis, degeneration and proliferation of the pigment epithelium occur, and patches of proliferated pigment are observed in and about the areas of choroidal involvement Choroidal hemorrhages are also frequently seen in cases of severe choroiditis They may occur anywhere in the region of the posterior pole but, unfortunately, are most often seen in and about the fovea Sometimes little irregular white lines are seen early in the disease These were shown by Salzmann<sup>127</sup> to be minute ruptures in Bruch's membrane and, according to him, are the gates through which the choroidal process invades the retina Less frequently, a black spot is seen at the macula First mentioned by Foerster, it was described by

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<sup>127</sup> Salzmann, M Die Atrophie der Aderhaut in kurzsichtigen Auge, Arch f Ophth 54 337-410, 1902



Fuchs in detail and is commonly called Fuchs's black spot. It was attributed to edema by Batten,<sup>115</sup> to hemorrhage by Collins and Mayou,<sup>128</sup> and to piling up of pigment by Coats,<sup>129</sup> who published a photomicrograph demonstrating his observations.

Atrophy of the retina is secondary to the changes in the choroid. With the degeneration of the choriocapillaris, the outer layers of the retina undergo atrophy, and with the degeneration of the elastic lamina, pigment invades the retina, and eventually fusion of the whole retina and choroid into a band of connective tissue results, just as in the scarring of chorioretinitis. Because the fovea is more dependent on the choroidal circulation, degeneration is often more advanced here. Vacuolation is seen microscopically, and the process may go on to formation of cyst or hole at the macula. Peripheral cystic degeneration of the retina is thought to come on earlier and to be more extensive in myopic eyes than in the normal eye. As a result of the distention of the globe, the retinal blood vessels are stretched and assume long, straight courses.

Microscopic study of myopic globes has added little to knowledge of the cause of the lesions. The degeneration of the choroid and retina can be seen in detail, but it cannot be differentiated from the degeneration following inflammatory processes. Infiltration of small white blood cells, plasma cells and lymphocytes has been described by Parsons<sup>118</sup> and Salzmann.<sup>127</sup> The structure of the crescents can be studied, the crescent of distraction is seen to be due to uncovering of the sclera by degeneration of the choroid in varying degrees. The crescent of supertraction is seen as a fold of retina and choroid, or portions thereof. The sclera is seen to decrease steadily in thickness from the equator backward, in contrast to the condition in the normal eye. It is thinnest at the posterior pole, where it may be one-third to one-fourth the normal thickness.

Extensive pathologic changes are seen in the vitreous in this condition. Opacities are nearly always present in the active stages of the choroidal process. With enlargement of the eye, the cavity of the vitreous is necessarily enlarged, and this increase can be compensated only by transudation of fluid into the vitreous, leading to degeneration and fluidity of this structure. Detachment of the vitreous at the disk is often seen and is said to be caused by the recession of the posterior pole. The degeneration of the vitreous is accompanied with degeneration of the zonular fibers. This may result in tremulousness of the lens and iris. In such eyes the lens may be luxated spontaneously or on slight trauma. Opacities in the lens, either small, discrete ones or full-blown cataract, may also accompany the degeneration of the vitreous.

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128 Collins, E., and Mayou, M. *Pathology and Bacteriology of the Eye*, Philadelphia, P. Blakiston's Sons & Co., 1925, pp. 111-121.

129 Coats, cited by Parsons,<sup>118</sup> p. 919.

## SIGNIFICANCE OF THE PATHOLOGIC CHANGES

In assessing the part played by these pathologic processes in the causation of myopia, the main point of debate is whether the lesions in the fundus cause the lengthening of the eye or the stretching of the globe causes the lesions of the fundus. The mechanistic theories favor the latter point of view, the proponents of sclerochoroiditis, the former. Study of the pathologic picture reveals that some of the most important lesions are unexplained by stretching. The staphyloma of the posterior pole presents the first stumbling block. It is conceivable that the generalized distention of the whole posterior portion of the eye might be the result of stretching, but the commoner type of localized ectasia, in which normal sclera passes suddenly into a thin, deformed tissue, cannot be explained by stretching.

The atrophic condition of the ciliary muscle is attributed to disuse, on the basis of the observation that most myopic persons do not accommodate. The absence of this atrophy in some myopic eyes is usually explained by emmetropia or hypermetropia in the other eye, forcing the person to accommodate. It is more likely that the correct explanation lies oftener in full correction of the myopia during life, with resulting normal use of the ciliary muscle. These changes in the ciliary body are the result of the refractive condition of the myopic eye and can be seen in both physiologic and pathologic myopia. Therefore they are not part of the pathologic picture of sclerochoroiditis.

The crescent is difficult to explain. Originally every one thought it was a phenomenon of the posterior pole caused by stretching, and some said it was merely part of the staphyloma. This idea of its association with the staphyloma has been discarded. Schnabel and Herrnheiser<sup>70</sup> and von Szily<sup>130</sup> proposed that the crescent was a congenital defect, not associated with myopia. Elschmig<sup>131</sup> stated the belief that it was a coloboma, due to persistence of the limiting tissue between the edge of the disk and the innermost part of the pia. Parsons<sup>132</sup> also favored the theory of a congenital defect. Ida Mann<sup>133</sup> differentiated the crescent of myopia from congenital defects and stated that it was due to a slow pathologic process in the eye. If the crescent were due to distraction of the retina and choroid from the disk, it would seem that it should all be white and should not exhibit the various degrees

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130 von Szily, A. Ueber den "Conus in heterotypischer Richtung," *Arch f Ophth* **110** 183-291, 1922.

131 Elschmig, A. Das Colobom am Sehnerveneintritte und der Conus nach unten, *Arch f Ophth* **51** 391-430, 1900.

132 Parsons, J. H. *Diseases of the Eye*, New York, The Macmillan Company, 1942, p 517.

133 Mann, I. *Developmental Abnormalities of Eye*, London, Cambridge University Press, 1937, p 110.

of progression, as seen in the changing colors. Further, one would not expect to see the crescent in small eyes that have not been stretched. Moreover, if the crescent were a congenital defect, one would not expect the colors to change during life. Clinical study of these crescents shows that there are all degrees of depigmentation, and thus of progression, and this observation favors Mann's theory of a pathologic process. However, the constancy of the form and shape of the crescent is against its being a purely inflammatory lesion. It seems to me that it is best explained by a combination of traction and a pathologic process. The tension on the choroid of the dilating globe is great at the posterior pole because of the insertion of the choroid into the disk, and, in the presence of weakening due to the choroidal disease, this particular part of the choroid may be prone to give way and leave the characteristic hammock defect in the choroid.

The crescent of supertraction appears to be the result of traction alone. As the globe distends at the posterior pole, there must be traction on the coats of the eye in the region of the posterior pole. The crescent of supertraction seems to be the result of this pull posteriorly. The sclera nasal to the disk is separated from the focal point of the disease process by the nerve itself, while the choroid and retina are subjected to the traction throughout their entirety.

The occurrence of the pathologic lesions in full-blown form in eyes of normal size, where stretching has been minimal or nil, is strong evidence against the mechanical school of thought. The occurrence of such extensive choroidal lesions, in itself, seems to rule against stretching, since one would not expect a tissue as elastic as the choroid to respond so drastically to tension. Further, if the choroidal lesions were due to stretching, why should they be confined to the posterior pole? It is difficult to conceive of a localized part of the choroid being stretched without affecting the rest of the choroidal tract. The late onset of the macular lesions is also evidence against stretching, they commonly come on after elongation of the eye has occurred. The infiltration of white blood cells is difficult to evaluate. Salzmann and Parsons expressed the opinion that this reaction is evidence of the irritative effect of the stretching of the globe rather than a definite sign of inflammation. This may be true, on the other hand, a similar reaction is commonly seen in sections of eyes with chronic chorioretinitis. It should be pointed out that almost the only slides of myopic eyes available for microscopic study are those of eyes removed for some other purpose, such as tumor, and often long after the active stage of the myopia. It would be of great value to study sections of myopic eyes of patients meeting death while the myopia is in the active stage. In favor of an inflammatory process are the following observations. Choroiditis is

often confined principally to the posterior pole, it usually, or perhaps always, instigates a concurrent scleritis, it is usually accompanied with opacities in the vitreous, and macular retinal changes are commonly secondary and subsequent to choroiditis. Thus, it would seem that, although some of the changes are due to traction of the distending globe, stretching per se cannot be accepted as the initial lesion in this disease.

Whether the process is an inflammatory or an atrophic one poses another problem. Fuchs<sup>134</sup> said the chorioretinal changes were definitely a pathologic process, but did not elaborate the idea. Troncoso<sup>135</sup> called the process "myopic choroidiosis" and attributed it to degeneration, following stretching of the globe, and later progressing to atrophy. The strongest evidence in favor of the inflammatory nature of the process is the clinical observation of cases in the active stage, the appearance is certainly not that of an atrophic process. It is difficult to explain the stretching of the sclera if atrophy of the choroid is accepted. The lowering of the intraocular pressure tends to support the theory of an inflammatory origin, in that this is a known accompaniment of uveal disease. It seems, therefore, that the bulk of evidence favors the inflammatory nature of the lesion and that the primary site lies in the choroid.

#### COMMENT

The very diversity and number of etiologic theories of the pathogenesis of myopia indicate that the problem has never been satisfactorily solved. It is difficult to account for the proposal of so many mechanical hypotheses, considering the extent of the possible pathologic changes in the myopic fundus. One can only say that too much emphasis has been placed on the element of axial elongation and that the other pathologic factors have been practically disregarded.

The theory that increased intraocular tension from excessive accommodation or convergence might cause distention of the globe has been refuted since it was first proposed. It is generally agreed that accommodation does not cause an increase in the ocular tension but, rather, is an aid in keeping the pressure within normal limits. Contraction of the extraocular muscles does cause some increase in the intraocular tension, but so little that it is not of any clinical importance. The difference between the pathology of myopia and that of glaucoma and buphthalmos seems to rule out increased tension of the eye, from any cause, as one of the etiologic factors in the production of axial elongation.

134 Fuchs, E. Textbook of Ophthalmology, translated by A. Duane, ed. 7, Philadelphia, J. B. Lippincott Company, 1924, pp. 193-204.

135 Troncoso, M. U. Internal Diseases of the Eye and Atlas of Ophthalmoscopy, Philadelphia, F. A. Davis Company, 1946, pp. 463-470.

That myopia is the result of mechanical wear and tear in convergence of the eyes, as proposed by Foerster and Jackson, is unlikely. The occurrence of myopia in one eye and not in the other, and its occurrence in one-eyed people and in persons without binocular single vision are all unexplained if this theory is accepted. The more frequent association of convergence excess with hypermetropia than with myopia furnishes another objection. The arguments against school myopia also refute this hypothesis.

Donder's and Cohn's idea of school myopia is as difficult to disprove as it is to prove. One objection is the absence of definite proof that school myopia exists. The incidence of myopia during the school years may well be a mere coincidence. Statistics are available to show its similar occurrence in children who do not go to school. The increasing incidence in particular school years and the fact that myopia does not increase in colleges and postgraduate schools are difficult to associate with the theory of school myopia as the cause. Further, Brown<sup>136</sup> has shown that the increased incidence of myopia in the early school years conforms to the cycle of refractive changes in the normal eye. If Cohn's facts were true, the incidence of myopia should have decreased with improved school conditions. Reports of decreased incidence have issued from Sweden, Denmark, Germany and Portugal, but for every one there is a contradictory report with equally impressive statistics. This is confusing, but there has been no positive proof that the incidence of myopia has decreased. To me a strong argument against school myopia is a negative one, namely, that the incidence of myopia has not increased along with the great increase in education and literacy during the past one hundred years, with its consequent increase in the use of the eyes for near vision.

Most of the remaining theories have little in their favor, usually there are as many ophthalmologists opposed to as concurring in them. Often there seems to be a confusion between cause and result. Thus, in axial myopia there is by definition an oversize of the globe, but that is no proof that it is a disorder of growth. Likewise, with the proposal of the congenital deficiency of the sclera. The sclera becomes thin, it is true, but it does not resemble a congenital defect. The fact that myopia is commonly progressive about the time of puberty is not proof that it is an endocrine disorder.

There are two etiologic theories that are difficult to refute. One is Steiger's biologic variation, and the other, von Graefe's sclerochoroiditis. Steiger's original hypothesis has been found wanting in some respects. He neglected to include the refraction of the lens in his calculations, and

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136 Brown, E. V. L. Use-Abuse Theory of Changes in Refraction Versus Biologic Theory, *Arch Ophth* 28:845-850 (Nov) 1942.

he considered the refractive errors as free variables. The result was a curve that differed from the normal curve in a peak that was too high (emmetropia) and in a prolongation of the myopic limb. It was shown by Tron that exclusion of myopic subjects with lesions of the fundus changed the myopic end of the curve to the normal symmetric type. Berg<sup>106</sup> has since demonstrated that if a curve, calculated not on free variables, but on three correlated factors, is constructed, the result closely resembles the actual distribution of refractive errors. Thus, with the exclusion of the type associated with pathologic changes in the fundus, it is likely that Steiger was right in his description of myopia as a biologic variation, and that Donders was wrong when he said that every myopic eye is a diseased eye. The eye with the lesions of the fundus, however, is a diseased eye, and it is necessary to consider it a clinical entity in view of the large number of cases encountered with the typical characteristics. The conclusion is inevitable, then, that one must abandon the monistic schema of myopia advocated by Jackson<sup>137</sup> and assume that there are two main types of myopia: one, a biologic variation, and the other a pathologic disease of the eye.

#### CLASSIFICATION

An obstacle to the study of myopia, whether etiologic, pathologic or clinical, is the lack of a generally accepted classification. It is obvious from the literature that many ophthalmologists believe there are two types of myopia, but few classify their cases in their discussions, and most use myopia as an all-inclusive term. The result is most confusing. The factor of heredity is a representative example. Many surveys showing varying frequencies of familial histories have been reported, but without any qualification as to type of myopia. In spite of all the work done on the heredity of myopia, it is still impossible to draw any reliable conclusions.

A number of classifications have been proposed. Donders<sup>7</sup> classified myopia as stationary, temporarily progressive and continuously progressive forms. This division is a clinical one, based on the refractive state, is not applicable to pathologic myopia and does not differentiate between the two types. Tscherning<sup>112</sup> and Fuchs<sup>134</sup> divided near sightedness into high and low myopia, and this classification has been sponsored more recently by Rodin<sup>138</sup> and Stocker,<sup>76</sup> in this country. This division is unsatisfactory for the same reasons, it does not describe the pathologic type, and it does not differentiate the two entirely different processes. Parsons<sup>118</sup> set forth an anatomic classification in his

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137 Jackson, E. Norms of Refraction, Tr. Sect. Ophth., A. M. A., 1931, pp. 174-190.

138 Rodin, F. H. Etiology of Myopia, Arch. Ophth. 9: 264-279 (Feb.) 1933.

textbook, based on the following factors axial elongation of the globe, increased curvature of the cornea or lens, increased refractive index of the various media, forward displacement of the lens and combinations of these factors This classification has been repeated in many textbooks, because the types cannot be diagnosed clinically, but, again, the pathologic form is not included Prangen,<sup>44</sup> in 1939, suggested two main types (1) developmental myopia, subdivided into curvature and axial forms, and (2) malignant myopia, of moderate and severe degrees This division is not favored, because one cannot differentiate curvature myopia and axial myopia in life, and because the word "malignant" has a bad connotation Koster<sup>139</sup> divided his cases of myopia into (1) a cyclitic type, with pathologic process in the fundus, and (2) an optic type, in which he considered the eye as sound as the emmetropic eye He pointed out the importance of differentiating the two states, both for prognosis and for therapy Sourasky<sup>121</sup> and Cowan<sup>124</sup> also vigorously sponsored this type of division but did not suggest specific terms

The best classification is probably the simplest Therefore it is suggested that there are two types of myopia (1) primary, or physiologic, myopia, and (2) secondary, or pathologic, myopia Primary myopia is, as far as is known at present, a biologic variation of refraction and a healthy one, with vision correctable to normal standards It includes myopia of both high and low degrees, the great majority of cases being of the latter type It is not possible to say whether the axial length or the refraction of the media is at fault, since either one can be within normal limits and still cause myopia Secondary myopia is the result of disease of the coats of the eye It should not be called myopia at all, but this term is proposed because of long-established custom and because the true cause is not known The differential diagnosis of the two forms rests on the observation of pathologic changes in the fundus The great majority of cases will be of the primary type, according to the meager statistics now available

The results that can be obtained from the use of such a classification in a large clinic are manifold The incidence of the two forms can be more definitely determined The range of myopic error in the two forms can be established The incidence of secondary myopia in previously emmetropic and hypermetropic persons can be studied Whether the pathologic form arises more often in cases of primary myopia than in cases of emmetropia or hyperopia will be a pertinent finding That conclusion, together with the continued use of this classification, will

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139 Koster, W Cyclitic Myopia, Optic Myopia, and Infantile Glaucoma, *Nederl tijdschr v geneesk.* 2 113, 1916, abstracted, *J A M A* 67 645 (Aug 19) 1916

demonstrate in time whether the classification is a valid one. The influence of heredity can be better studied by dividing the cases into two types. Better study and treatment of the pathologic form will evolve as a result of its separation from the errors of refraction. It is not intended that this classification is the final answer to the problem of myopia, but it is suggested that a statistical study will give much more information about myopia, when other approaches have failed.

#### CONCLUSIONS

1 Axial elongation of the eye beyond normal limits is not necessary to myopia.

2 Near work has never been shown to cause myopia, either in school or in adult occupations.

3 There is no proof that overcrowding, poverty, poor health, inferior or superior mentality or bad ocular hygiene can cause myopia.

4 No mechanical basis for myopia has ever been substantiated.

5 There is no evidence that congenital deficiency of the sclera, disorder of growth, imbalance of the extraocular muscles, endocrine dysfunction, or avitaminoses plays any part in the causation of myopia.

6 The relation of other diseases to pathologic myopia has not been determined. It is possible that they play a part in the production of secondary myopia.

7 The role of heredity is not definitely established, particularly with respect to secondary myopia.

8 There are statistical evidence that primary myopia is a biologic variation and clinical evidence that it is a healthy refractive state.

9 There is clinical and pathologic evidence that secondary myopia is a disease of the eye, the cause of which has not been demonstrated. It is suggested that a low grade chronic choroiditis is the primary lesion.

10 The main factor in differential diagnosis of the two types of myopia is the presence or absence of the lesions in the fundus.

11 A classification of myopia is essential for progress in statistical and clinical research on this condition. The terms primary and secondary are suggested as simple and descriptive.

12 Differential diagnosis of the two types is of great importance clinically, in therapy and in prognosis. It will prevent the waste of many useful citizens as "myopic cripples."



# CRANIAL EPIDERMOID WITH EROSION OF THE ROOF OF THE ORBIT

Report of a Case

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AND

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THE FIRST primary cranial epidermoid was reported by Johannes Muller<sup>1</sup> in 1838. He called attention to the resemblance between cells of epidermal origin and the cells observed in these tumors. Remak, in 1854, advanced the theory of ectodermal rests to explain the origin of epithelial tumors having no attachment to the surface epithelium. Bostroem,<sup>2</sup> in 1897, first used the term epidermoid and pointed out the many opportunities for bits of ectoderm to be pinched off during closure of the neural tube and during subsequent stages in the development of the central nervous system, as when the transverse folds are forming. He expressed the belief that only cell rests in contact with the pia or lodged in the diploe are assured of nourishment adequate to develop into tumors. He stated that when cells destined only for the epidermis are pinched off they give rise to tumors exhibiting only epidermoid structures. When deeper layers are also included, a dermoid develops, containing hair and skin glands as well.

The term primary epidermoid is used to distinguish this tumor from collections of epithelial debris, called acquired cholesteatoma, which are observed, for example, in the ear after an infection. The term cranial distinguishes this type from the intracranial epidermoids. In the case of the epidermoids originating in the diploe of the flat bones of the skull, the increasing size of the tumor causes expansion of the overlying bone, and finally erosion, giving the typical roentgenographic picture. Bucy<sup>3</sup> called attention to the importance of noting the erosion of the inner table of the skull, as sometimes this erosion is only pinpoint in size and beyond

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Read at a meeting of the Section of Ophthalmology of the New York Academy of Medicine, Feb 17, 1947. An abstract of this paper, with discussion was published in the October 1947 issue of the ARCHIVES, pages 552-554.

1 Müller, J. Ueber den feinern Bau und die Formen der krankhaften, G. E. Schwülste, Berlin, G. Reimer, 1838.

2 Bostroem, A. Centralbl f allg Path u path Anat 8 1, 1897.

3 Bucy, P. C. Intradiploic Epidermoid (Cholesteatoma) of Skull, Arch Surg 31 190 (Aug) 1935.

it a larger mass of tumor may have developed between the skull and the dura. He pointed out that these minute defects may represent the persistence of the opening through which an abnormal prolongation of the papillary layer of the epidermis remained attached to the dura during the formation of the flat bones of the skull, namely, the frontal, parietal, occipital and temporal bones.

The cranial epidermoid does not infiltrate and so merely displaces brain tissue, but even though the outer layers of the tumor are friable, its growth is so inexorable that it will erode and destroy any unyielding tissue with which it may come in contact, including bone. The growth is well encapsulated and is covered with layers simulating the skin of an onion. These layers constitute the lining of the mass. The outer layer is chiefly of acellular connective tissue, under this are a middle layer, composed of stratified squamous epithelium, and an inner layer, formed of cornified epithelium.

Cushing, in a series of 2,004 cerebral tumors, found that only 0.6 per cent were epidermoids. He was one of the first to associate defects in the bones of the skull with epidermoids.<sup>4</sup> To date, 188 cases of cranial epidermoid have been reported. Thirty-three of the tumors were the diploic type, to which the tumor we describe here belongs. The site of election of the intracranial type is along the base of the brain and the brain stem. Over 12 per cent occurred within the ventricles. Whereas epidermoids may occur at any age, men seem to be affected more frequently than women.

#### REPORT OF A CASE

*History and Examination*—M. N., a man aged 84, first presented himself on Oct. 22, 1946, complaining that although he had had a mass in the left frontal region all his life, for the past three years it had grown to the extent that he could not open his left eye. Examination of the right eye revealed a normal condition except that early sclerosis of the lens had reduced his vision to 20/30 with correction. In the left frontal region was a mass the size of a small apple, which fluctuated and transmitted the intracranial pulsation (fig. 1A). On deep palpation around the mass, the edge of the bone could be felt, suggesting absence of the frontal bone. The lid could not be raised voluntarily, and the wall of the cyst could be felt pushing the tissues of the upper lid forward. On raising the left upper lid with the finger, one noted no elevating action of the eyeball. Intraocular examination showed nothing significant except for an immature cataract. Vision here, however, could be improved to 20/50.

Roentgenograms confirmed the complete loss of the bone in the region of the cyst and suggested absence of the roof of the orbit, the latter having been suspected on clinical grounds because of loss of ability to elevate the globe (fig. 2).

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<sup>4</sup> Cushing, H. A Large Epidermal Cholesteatoma of Parietotemporal Region Deforming Left Hemisphere Without Cerebral Symptoms, *Surg., Gynec. & Obst.* 34: 557 (May) 1922.

*Operative Procedure*—On December 4, Dr Henry Wigderson operated, with the use of local anesthesia. A U-shaped incision was made in the skin within about 1 cm of the tumor. The base of the cutaneous flap was in the supraorbital region. The flap was dissected and stripped rather freely. The tumor remained covered with periosteum. An incision was then made through the periosteum down to the bone in the region of the margin of the bony defect along its superior border. In this way the tumor was dissected free from the bone, and the typical smoothly scalloped edge of the bony deformity produced by the epidermoid



Fig 1—*A*, preoperative appearance of the patient, showing an epidermoid producing closure of the lid, *B*, postoperative appearance.



Fig 2—Typical roentgenogram, showing loss of bone in the frontal area, as well as in the orbit

was revealed. The tumor was dissected away from the edge of the bone for a distance of about 5 to 6 cm. At this stage the capsule was torn. An effort was made to maintain the tumor in a fairly intact state and to continue the dissection, but this attempt was unsuccessful. The capsule was then incised widely, and the contents, consisting chiefly of 75 cc of caseous-looking material and a yellowish, oily fluid, evacuated. The upper part of the capsule was cut away. The capsule remained adherent to the underlying dura. Some of this was stripped free, but in order that the dura might not be torn in the process, and in view of

the age of the patient, it was not attempted to remove the capsule completely. After the tumor had been removed, the bony deformity was observed as follows: There was a defect measuring approximately 7 cm in diameter in the left frontal region. In the superolateral two thirds the bony edge was beveled. In the medial third the bone was undermined and somewhat elevated. The pulsating dura was observed at the base of the tumor cavity. Anteriorly, the supraorbital ridge and the anterior two thirds of the roof of the orbit had been destroyed (fig 3). When the patient was asked to look up, the fascial roof of the orbit was retracted, and when he was asked to look down, it moved upward. A Penrose drain was brought out through a stab wound posteriorly. The skin was closed with a continuous modified Steward stitch. A large bony defect and redundancy of skin remained. The postoperative course was uneventful.

*Histologic Study*—The lining of the wall of the cyst showed epithelial cells suggestive of the stratum granulosum (fig 4). The cystic fluid contained cholesterol crystals.

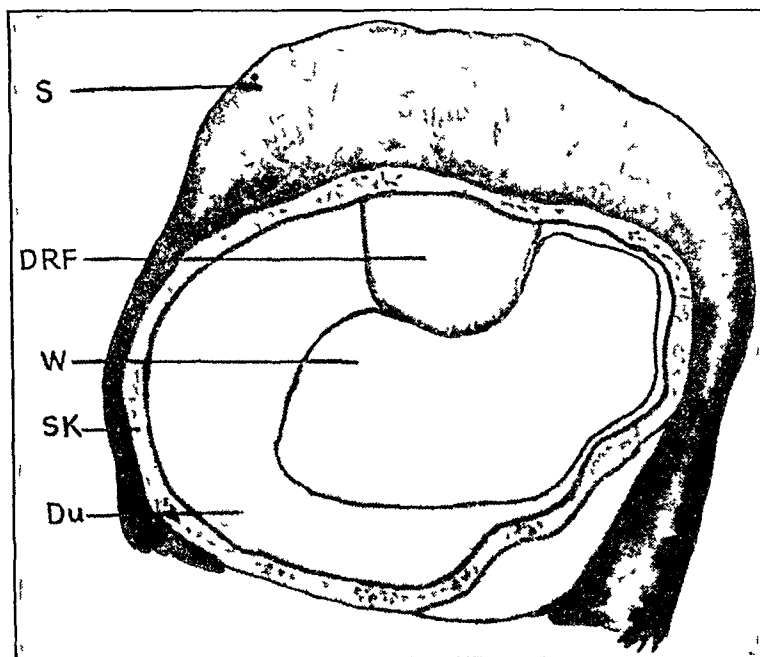


Fig 3—Appearance of the operative field at the conclusion of the operation. Here, *S* indicates scalp, *DRF*, defect in roof of orbit, *W*, wall of cyst, *SK*, defect in skull, and *DU*, dura.

*Postoperative Course*—Reexamination on Feb 17, 1947 disclosed that the palpebral apertures were of equal width (8 mm) (fig 1 *B*). Corneal hyposensitivity was present in the left eye. No limitation of elevation of the globe was present, and the return of function was complete. With the stethoscope over the eyeball, normal breath sounds were heard over the right eye, but sonorous breath sounds were heard over the closed left eyeball. With the exophthalmometer at 103 mm, the right eye measured 16 mm and the left eye 14 mm. In the cover test, exophoria for 13 inches (33 cm) measured 2  $\Delta$ , and fusion was present.

#### COMMENT

Although Cushing advised complete removal of the wall of the cyst in order to prevent recurrence, the slow growth of the tumor in the

present case together with the adherence to the dura and the age of the patient, justified conservatism in surgical procedure Cairns<sup>5</sup> reported 2 cases in which operation had been performed over seven years before, with only partial removal of the cyst wall, and no sign of recurrence had appeared

The movement of the fascial roof of the orbit as observed on the operating table should be given some thought, so that the normal physi-

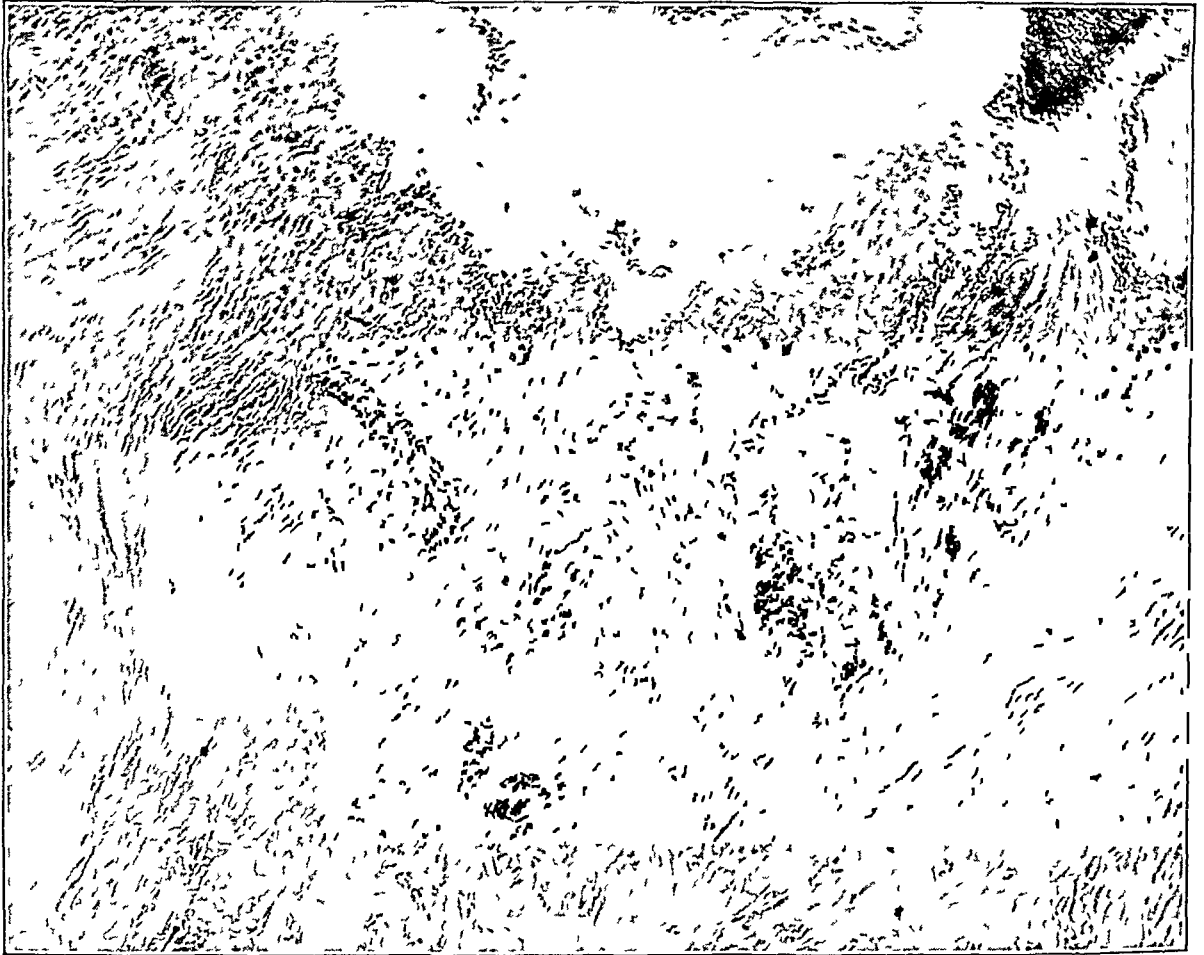


Fig 4—Photomicrograph, showing the epithelial cells lining the wall of the cyst  $\times 140$

ology of orbital movements as they are understood at present may be confirmed or corrected

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5 Cairns, H Ultimate Results of Operations for Intracranial Tumors  
Study of Series of Cases After Nine Year Interval, Yale J Biol & Med 8 421  
(May) 1936

## NORMAL OPTIC NERVE

### I Classification of the Optic Disk Based on Branching of the Central Retinal Artery

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IT HAS long been obvious that inadequate attention has been paid to the detailed topography of the eyegrounds. The older works called attention to general relations, and Goldstein<sup>1</sup> even suggested that photography of the fundus might be useful in identification of criminals. Jensen<sup>2</sup> studied distribution of vessels in the fundus in general. In a recent paper, Cordes<sup>3</sup> reviewed the congenital and acquired anomalies of the optic disk but did not make a detailed study of the distribution of vessels on the disk itself. Opportunity was recently afforded me to study the normal topography of the eyegrounds in several hundred men in the armed forces. The first phase of this study was limited to the relation of the retinal arteries to the quadrants of the optic disk. A planned study of this limited scope seemed particularly worth while because of the relations of these root vessels to changes in the nerve and vessels associated with glaucoma, to swelling of the optic nerve, a possible complication of arteriosclerosis, and to a number of other conditions which need not be recited.

After examination of hundreds of normal eyegrounds, it became apparent that there are several definite and easily recognizable variations in the distribution of the vessels as they emerge from the optic nerve head. It is interesting to note the position of the vessels as they appear in the normal eye. The present paper is concerned with a simple classification of the nerve head based on the branching of the central artery of the retina.

The classification is made by dividing the surface of the nerve head into four quadrants, i e., the upper and lower nasal and the upper and lower temporal. Since there are four main branches of the retinal artery, namely, the superior and inferior temporal and the superior and inferior nasal, there are nine possible variations in the distribution of these

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1 Simon, C, and Goldstein, I. New Scientific Method of Identification, New York State J Med **35** 901-906 (Sept 15) 1935

2 Jensen, V A, in Kershner, C M. Blood Supply of the Visual Pathway, Boston, Meador Publishing Company, 1943, pp 64-74

3 Cordes, F C. Congenital and Acquired Anomalies of the Optic Disk, Arch Ophth **23** 1063-1089 (May) 1940

vessels over the surface of the optic nerve head. These variations comprise the first nine classes. There is also a tenth class, in which the vessel does not follow the quadrant distribution. The distribution of the veins is disregarded in the makeup of this classification. The ten classes are described as follows:

- Class 1 Nasal  
All branches on nasal side of the disk
- Class 2 Nasal Oblique  
Superior vessels in upper nasal quadrant, inferior vessels in lower temporal quadrant
- Class 3 Temporal Oblique  
Superior branches in upper temporal quadrant, inferior branches in lower nasal quadrant
- Class 4 Temporal  
All branches on temporal side of disk
- Class 5 Nasal—Temporal Up  
Inferior branches in lower nasal quadrant, superior nasal branches in upper nasal quadrant, superior temporal branches in upper temporal quadrant
- Class 6 Nasal—Temporal Down  
Superior branches in upper nasal quadrant, inferior nasal branches in lower nasal quadrant, inferior temporal branches in lower temporal quadrant
- Class 7 Temporal—Nasal Up  
Inferior branches in lower temporal quadrant, superior nasal branches in upper nasal quadrant, superior temporal branches in upper temporal quadrant
- Class 8 Temporal—Nasal Down  
Superior branches in upper temporal quadrant, inferior nasal branches in lower nasal quadrant, inferior temporal branches in lower temporal quadrant.
- Class 9 Symmetric  
One branch in each quadrant
- Class 10 Miscellaneous

#### VESSELS OF INDETERMINATE QUADRANT DISTRIBUTION

The nomenclature of the ten classes of optic nerve heads was based on the five general types which appear: (1) the symmetric group, in which each quadrant contains a branch, (2) the nasal groups, in which all vessels are on the nasal side, (3) the temporal groups, in which all vessels are on the temporal side, (4) the oblique groups, in which the superior portion of the axis provides the name—for example, in class 3 (the temporal oblique), the superior branches appear in the upper temporal quadrant and the inferior branches in the lower nasal quadrant, and (5) the miscellaneous group. Classes 5 through 8 do not adhere to the strict types of vascular distribution and are named for the dominating type, with the second component in the name indicating the

branch which does not belong to the main type. For example, in class 5 the nerve head has branches in both nasal quadrants, hence, it is named nasal, and it also has a branch in the upper temporal quadrant which deviates from the nasal type, so the class is named nasal—temporal up. The miscellaneous group does not fit into any of the aforementioned types.

#### PROCEDURE

The eyegrounds of every person who came to the ophthalmic clinic of a large Army general hospital were examined routinely for pathologic changes prior to refraction. During this examination the classification of the disk was determined by simple inspection of the disk. In most instances there was no difficulty whatever in determining the classification of the disk, at least for the first nine classes. In cases in which there was a question as to whether or not a branch was in the nasal or in the temporal quadrant because it crossed the disk near the division, a streak of light from an ophthalmoscope was directed to the vertical diameter of the

TABLE 1—*Classification of 500 Optic Disks by the Distribution of Arterial Branches*

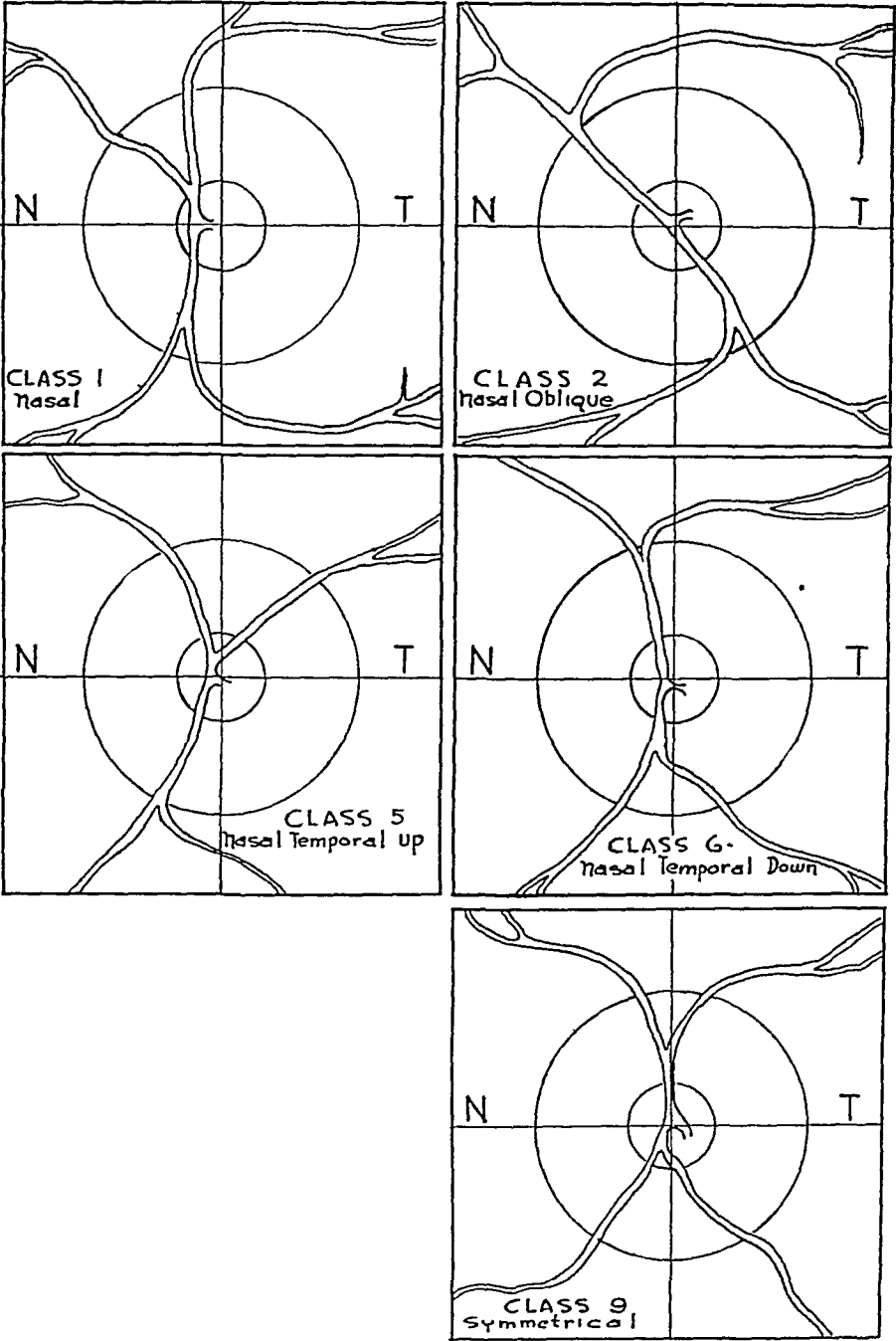
Class	First 200 Eyes		Second 200 Eyes		Last 100 Eyes		Total	
	No	%	No	%	No	%	No	%
1 Nasal	30	15	34	17	19	19	83	16.6
2 Nasal oblique	0	0	0	0	1	1.0	1	0.2
3 Temporal oblique	0	0	1	0.5	0	0	1	0.2
4 Temporal	0	0	0	0	0	0	0	0
5 Nasal—temporal up	73	36.5	71	35.5	32	32	176	35.2
6 Nasal—temporal down	16	8	18	9	12	12	46	9.2
7 Temporal—nasal up	0	0	2	1	1	1	3	0.6
8 Temporal—nasal down	0	0	0	0	0	0	0	0
9 Symmetric	71	35.5	63	31.5	26	26	160	32
10 Miscellaneous	10	5	11	5.5	9	9	30	6
Total	200	100	200	100.0	100	100	500	100

disk and a more careful observation made as to the exact class in which a particular disk should be placed. There was seldom any difficulty with regard to the upper and lower halves. More difficulty arose in distinguishing between the first nine classes and the so-called miscellaneous class, or class 10. It became very nearly a matter of personal judgment as to whether some disks should be placed in class 9 or class 10. Disks which had a large physiologic cup far to the temporal side, with vessels circling the edge of the disk, rather than branching on its surface, were those considered to be in class 10. As will be seen from the statistics which follow, such disks are not uncommon in persons with normal eyes, since approximately 10 per cent of the eyes studied had disks which appear in this class. It will be noted later that Sergeant Kestenbaum found a larger percentage of disks in class 10 than I did. In my opinion, the reason for this discrepancy is that he was not careful enough in distinguishing the exact difference between the first nine classes and the miscellaneous class, or class 10.

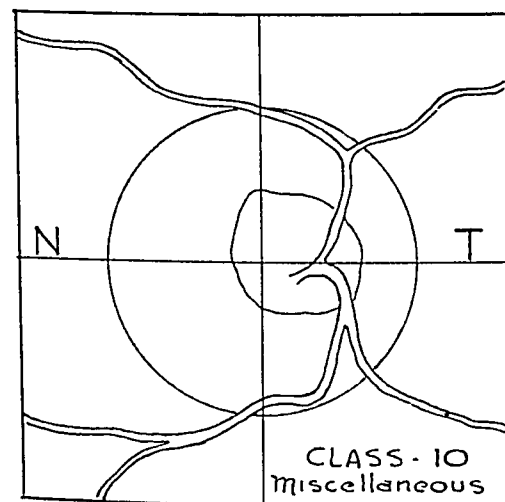
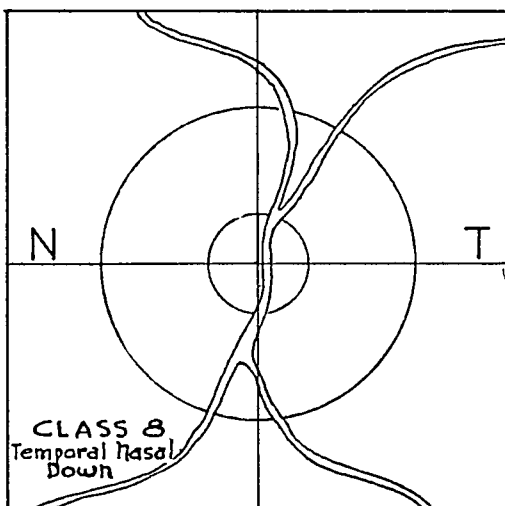
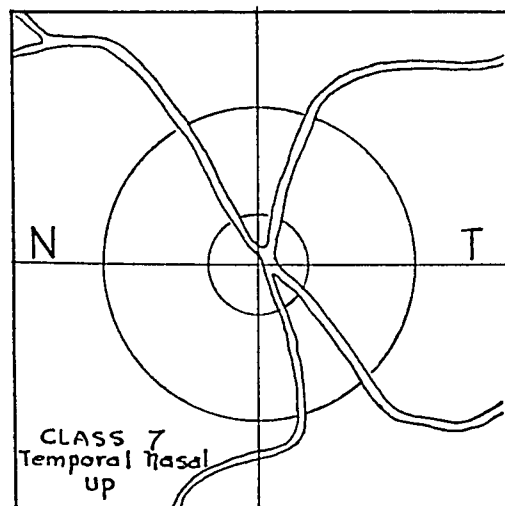
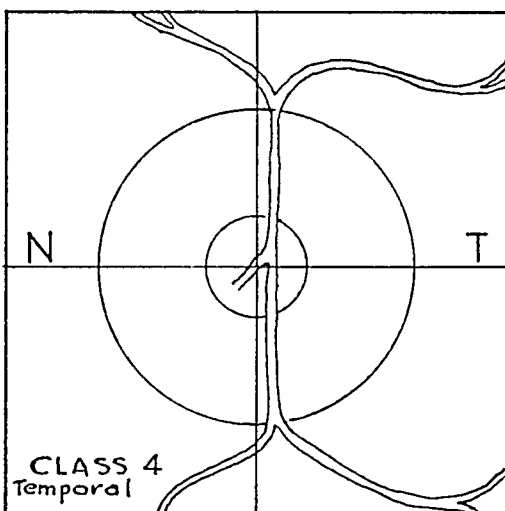
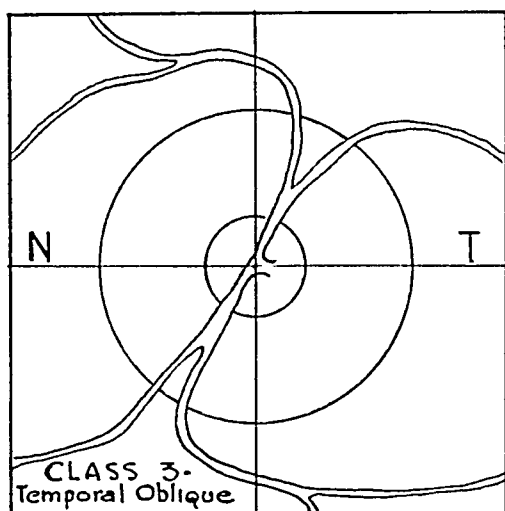
#### STATISTICAL ANALYSIS

A statistical analysis of 500 eyes, based on this classification, is shown in table 1. It will be noted that the classes in which the nasal





Normal optic nerve head, showing ten types of distribution of the branches of the central retinal artery



quadrants were devoid of main vascular branches were greatly in the minority. In other words, almost invariably there were vessels and their branches on the nasal side of the optic disk. Frequently, either the lower or the upper temporal quadrant was devoid of main branches of the retinal arteries. It is interesting to note that in this series of 500 eyes not a single one was placed in class 4, in which the vessels are on the temporal side of the disk, or a single one in class 8, in which the superior branches are in the upper temporal quadrant and the inferior branches in the nasal and temporal quadrants, respectively. Six per cent of the 500 eyes were placed in class 10, in which the optic

TABLE 2—*Tabulation of Individual Characteristics of the Optic Disks of 250 Subjects*

	First 100 Eyes		Second 100 Eyes		Last 50 Eyes		Total	
	No	%	No	%	No	%	No	%
Eyes both in same class	53	53	39	39	12	24	104	41.6
Eyes in different classes	47	47	61	61	38	76	146	58.4
Total	100	100	100	100	50	100	250	100.0

TABLE 3—*Classification of 324 Optic Disks by Distribution of Arterial Branches\**

Class	200 Eyes		124 Eyes		Total No. of Eyes (324)	
	No	%	No	%	No	%
1 Nasal	75	37.5	33	26.6	108	33.3
2 Nasal oblique	1	0.5	0	0	1	0.3
3 Temporal oblique	1	0.5	1	0.8	2	0.6
4 Temporal	0	0.0	0	0	0	0.0
5 Nasal—temporal up	24	12.0	16	12.9	40	12.2
6 Nasal—temporal down	19	9.5	8	6.5	27	8.3
7 Temporal—nasal up	4	2.0	2	1.6	6	1.8
8 Temporal—nasal down	2	1.0	1	0.8	3	0.9
9 Symmetric	19	9.5	6	4.8	25	7.6
10 Miscellaneous	55	27.5	57	46.0	112	35.0
Total	200	100.0	124	100.0	324	100.0

\* The statistical data in this series were obtained by Sgt. William Kestenbaum.

cup is very large, in many instances quite deep and much farther toward the temporal side of the disk than the cups in the other classes.

Another interesting feature of the analysis is that 16.6 per cent, or 83, of the 500 eyes fell in class 1, in which all the branches appear on the nasal side of the disk, surprisingly, only 160 of 500 eyes, or 32 per cent, fell in class 9, in which the branches are distributed in all four quadrants. The next most frequent occurrence was class 5, in which the lower nasal and the two upper quadrants contain the main branches of the vessels.

Table 2 presents a comparison of the two eyes of the 250 subjects which made up the statistical data for table 1. There were 104 subjects,

or 41.6 per cent, whose optic disks fell in the same class and 146 subjects, or 58.4 per cent, whose optic disks fell in different classes

Having obtained these data, I was not satisfied to use my own observations only in arriving at statistical conclusions. I had Sgt William Kestenbaum, an optometrist, with whom I was associated in the ophthalmic department of an Army general hospital, make a similar study. His series comprised 324 eyes, or 162 subjects. His results, though not exactly the same as mine, bear out the general distribution in a remarkably similar fashion. Tables 3 and 4 present his figures. The most interesting feature of his observations is that the disks of 72, or 44 per cent, of his patients fell in the same class and the disks of 90, or 56 per cent, in different classes.

Two other observations were made during this study. 1. The retinal artery emerges from the disk on the nasal side of the retinal vein. To date, I have seen only 1 case in which the retinal artery emerged temporal to the vein. 2. It is possible to recognize the vascular pattern and to classify the optic disk on this basis as long as

TABLE 4—*Tabulation of Individual Characteristics of Optic Disks in 162 Subjects\**

	100 Eyes		62 Eyes		Total	
	No	%	No	%	No	%
Both eyes in same class	49	49	23	37.1	72	44
Eyes in different classes	51	51	39	62.9	90	56
Total	100	100	62	100	162	100

\* The series was studied by Sgt William Kestenbaum

three hours after death. I had several opportunities to observe the eyegrounds immediately after death and to check them at frequent intervals up to the time when the arterial pattern was no longer visible because of postmortem changes. In none of the eyegrounds examined could the arterial distribution be seen after the three hour period.

#### CONCLUSIONS

1. The normal optic disk may be classified into ten distinct types, based on the distribution of the main branches of the central retinal artery.

2. It is extremely rare to find either the upper or the lower nasal quadrant devoid of main branches of the central retinal artery.

3. Up to the time of writing, no case has been found in which the whole nasal half of the disk was devoid of the main branches of the central retinal artery.

4. Less than one-half the 412 subjects studied had optic disks which were in the same class.

5 The arterial pattern of the eyegrounds can be recognized at least up to three hours after death

6 The central artery of the retina emerges from the disk on the nasal side of the central vein in a large majority of all eyes

Dr John N Evans rendered valuable assistance in the preparation of this paper, Sgt William Kestenbaum gathered the statistical material, and Mr Robert S Richards gave technical assistance in the composition of the diagrammatic sketches illustrating the paper

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# EFFECT OF ROENTGEN THERAPY ON EXPERIMENTAL OCULAR VACCINIA IN NONIMMUNE AND IN PARTIALLY IMMUNE RABBITS

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ACCIDENTAL ocular infection with vaccinia occurs usually as a complication of prophylactic immunization against smallpox. Rarely infection results from a laboratory accident during the preparation or experimental use of the virus. The danger of ocular infection lies in involvement of the cornea, with subsequent development of an opaque scar.

The prevention of permanent impairment of vision is a goal in treating any infection of the eye. The therapy of ocular vaccinia is not standardized. Various forms of radiation therapy have been used in human beings and in rabbits. The present experiments were suggested by the beneficial results obtained from the use of roentgen therapy for an accidental ocular infection in a partially immune human being.<sup>1</sup>

## EXPERIMENTAL STUDY

Rabbits were used to study the effect of direct irradiation at different stages of ocular vaccinia in nonimmune and partially immune animals and the nonspecific effect of irradiation of a distant primary lesion.

## MATERIALS AND METHODS

Glycerinated calf lymph virus containing brilliant green was obtained from the North Carolina State Department of Health. All the virus used in the preliminary

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From the Departments of Internal Medicine, Physiology and Pharmacology, and Radiology, Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital.

1 Pittman, H W, Holt, L B, and Harrell, G T. The Effect of Irradiation, Immunity and Other Factors on Vaccinia Infection. A Review Illustrated by the Report of a Secondary Ocular Infection Treated with Roentgen Rays, *Arch. Int. Med.* 80:61-67 (July) 1947.

experiments was from the same lot, and that used in subsequent experiments was from another lot, the virus was stored in sealed capillary tubes in a refrigerator at 8 C

One hundred and six rabbits, of both sexes, were used. The majority of the rabbits were from 2 to 4 months old, but a few rabbits in the control groups were older. All the females were kept in individual cages, some of the males in later experiments were grouped together. All animals were maintained on a stock diet ("Kasco complete rabbit ration," Kasco Mills, Inc., Toledo, Ohio) for at least eight days before the experiments were started. The animals were fed and watered at regular intervals, usually twice daily, to insure adequate nutrition and hydration.

Ocular anesthesia was obtained by instilling in the conjunctival sac two drops of a 2 per cent aqueous solution of butacaine sulfate U S P. Fifteen minutes later three superficial vertical scratches were made on the anesthetized cornea with a sterile sewing needle. One drop of virus was placed in the conjunctival sac, and the lid was closed, opened and reclosed in order to spread the virus over the entire cornea. The eyelid was always handled with the greatest care to avoid abrasion of the palpebral conjunctiva. Only one eye was inoculated in each rabbit.

The left flank of each rabbit which received inoculation in the skin was cleared of hair with animal clippers. Inoculation was performed by the combined technique of linear scratches and multiple punctures of the skin.

In preliminary experiments, roentgen therapy was administered with the following factors: 100 kilovolts, 5 milliamperes, distance 20 cm, portal diameter 2.5 cm, no filter except the 0.5 mm of aluminum inherent in the tube, exposure, thirty seconds. The half value layer equaled 0.80 mm of aluminum. All animals except those in group A were treated three times, and thus received 102 r in air per treatment, because of technical difficulties the rabbits in group A received only two treatments. In subsequent experiments the factors were slightly altered, so that 120 kilovolts at a distance of 21 cm was used, the half value layer then equaled 0.94 mm of aluminum, and the animals received 105 r in air at each treatment.

The eyes of all animals in the preliminary (qualitative) experiments were examined daily for lacrimation, exudate, vascular engorgement, edema, corneal ulcers and opacities, miosis, blepharitis, iritis and pannus, the flanks were examined for edema, erythema, macules, papules, vesicles and pustules. The reactions were graded on a scale of 1 to 6 plus. The animals were observed daily for twenty-eight days, and then at irregular intervals for fifty-three days in experiment 1 and for thirty-six days in experiment 2. In subsequent (quantitative) experiments (3A and 3B) the animals were observed for sixteen days, and only for opacity of the cornea. The degree of corneal opacity was graded at the time the animals were killed.

Observation of the extent of the ocular lesion is a rough estimation of damage, but gives no information on the degree of impairment of vision. In order to measure objectively the decrease in transmission of visible light in the cornea of an experimental animal, it was necessary to devise a quantitative method. A technique employing the photoelectric colorimeter was developed.<sup>2</sup> In experiment 3 the corneas of the infected and uninfected eyes of each animal were removed at the time the rabbit was killed. The control animals in group L were killed on the twenty-first day, and beginning on the twenty-fifth day animals were killed in multiples of five, 1 animal from each of the five test groups (J, K, M, N and O).

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2 Little, J. M., Mankin, J. W., Reid, C. H., and Harrell, G. T. The Scatter and Absorption of Light by the Excised Cornea at Various Wavelengths Determined by a Photoelectric Method, *J. Clin. Investigation* 26:416 (May) 1947.

## PRELIMINARY EXPERIMENTS

*Experiment 1 Determination of the Optimum Time for Roentgen Therapy of Primary Vaccinia of the Cornea in Nonimmune Rabbits*—Four groups consisting of 3 animals each, and another consisting of 2 animals, were used. In group A the treatments were given twenty-four and forty-eight hours after inoculation (as soon as secondary inoculation in a patient would be suspected, and before any lesion would have appeared), in group B the treatments were started at the time of appearance of the earliest visible lesion (vesiculation) and were given sixty-six, seventy-eight and ninety hours after inoculation, the rabbits in group C received treatment at the height of the lesions—one-hundred-sixty-eight, one-hundred-eighty and one-hundred-ninety-two hours after inoculation. The corresponding times for therapy will not necessarily occur at the same intervals after inoculation in human subjects, since vaccinia runs a more rapid course in rabbits than in human beings.

The rabbits in group D received no radiation and served as a control on the effect of roentgen therapy. Group E, consisting of 2 rabbits, served as a control on the extent of damage done by trauma, irradiation and chemical irritation. The corneas of both animals were anesthetized, but no vaccine was applied. The cornea of one animal was irradiated but not scarified, and that of the other was scarified but not irradiated.

**Results** All rabbits in groups A, B, C and D showed violent inflammatory reactions of the cornea and bulbar conjunctiva, beginning on the third day after inoculation and reaching a peak in the second week. The range in severity of the reactions in each group was moderately wide. The lesions subsided by the end of the third week, leaving in every instance an opacity of the cornea. In the rabbits of group A, irradiated on the first two days after inoculation, the lesions appeared one to one and one-half days later than in the controls (group D), but the peak of the reaction was reached at the same time. At the height of the process no appreciable difference between the irradiated lesions and those which had not been irradiated was detected. As the inflammatory process began to subside, between the ninth and the eleventh day, it became apparent that the acute lesions regressed more rapidly in the irradiated group (fig 1) and that the severest chronic lesions occurred in the corneas of the animals which had not been irradiated (fig 2). The slightest residual opacities were noted in group C, which received roentgen therapy at the height of the lesion. Figure 3 illustrates the best and the worst results in this group and in group D, in which the rabbits were untreated. The animals in groups A and B also showed less corneal opacity than those in group D. No visible lesions resulted from anesthesia, scarification or irradiation (group E). When the lesions at



twenty-eight days are scored from 1 to 6 plus, the difference between the means for the opacities of group C and D, or between the opacities of groups A, B, C together and those of group D gives a relative deviate of  $t$  which is statistically significant<sup>3</sup> (table 1)<sup>4</sup>

One rabbit in group A died on the thirteenth day of the experiment, 2 rabbits in group B died on the twenty-third and twenty-fifth days, respectively. The cause of death of the last 2 animals was not defi-

TABLE 1—*Statistical Comparison of Sums of Scores of Opacities (Experiment 1)*

Days	Groups Compared	n	Calculated Value for $t$	Significant Value for $t$ (5%)	Interpretation
7	ABC and D	10	1.11	2.228	Not Significant
	C and D	4	0.45	2.776	Not Significant
14	ABC and D	9	1.12	2.262	Not Significant
	C and D	4	0.54	2.776	Not Significant
21	ABC and D	9	1.12	2.262	Not Significant
	C and D	4	1.23	2.776	Not Significant
28	ABC and D	7	3.74	2.365	Significant
	C and D	4	3.43	2.776	Significant

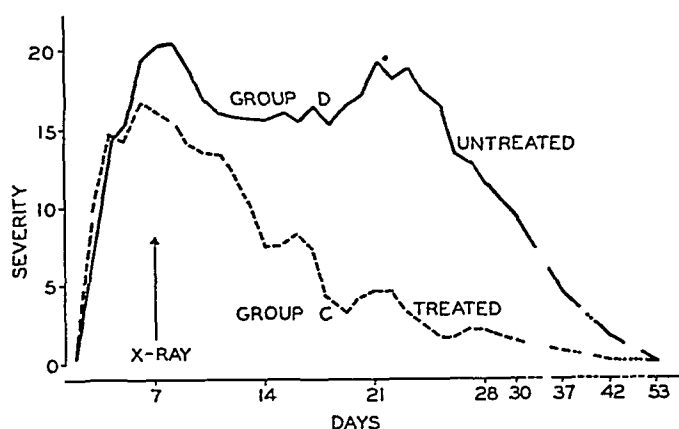


Fig 1—The mean of the sums of the scores of all acute lesions of the eye in group C (treated with roentgen radiation) and group D (untreated) are plotted as three point moving averages. The curves for groups A and B (also treated with roentgen radiation, but at slightly different intervals after inoculation) closely followed that for group C.

nitely determined, but in no instance was death thought to be due to generalized vaccinia or to an overdose of roentgen radiation.

*Experiment 2—Role of Partial Immunity in Ocular Vaccinia. A Effect of Direct and Distant Roentgen Therapy on Secondary Vaccinia of the Cornea in Animals Partially Immune as a Result of Primary Inoculation of the Skin*—The flanks of 6 rabbits were inoculated with vaccinia virus, seventy-two hours later,

3 Dr Nash Herndon assisted in the statistical criticism.

4 Snedecor, C. W. *Statistical Methods*, Ames, Iowa, Iowa State College Press, 1940.

after the local lesions had appeared in the flanks, the corneas were inoculated with fresh virus. Group F, consisting of 3 rabbits, received roentgen treatments to the eye one hundred and thirty-six, one hundred and forty-eight and one hundred and sixty-eight hours, respectively, after inoculation of the flank (two and a

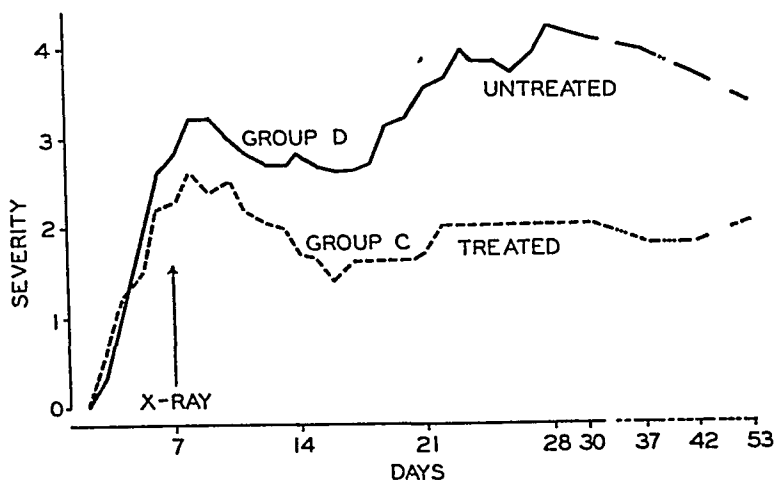


Fig 2—The mean of the sums of the scores of corneal opacities—the only chronic lesion—in group C (treated with roentgen radiation) and group D (untreated) are plotted as three-point moving averages. The curves for groups A and B (also treated with roentgen radiation, but at slightly different intervals after inoculation) closely followed that of group C until twenty-one days after inoculation. They then gradually rose until the twenty-eighth day and thereafter remained parallel to the curve for group C.

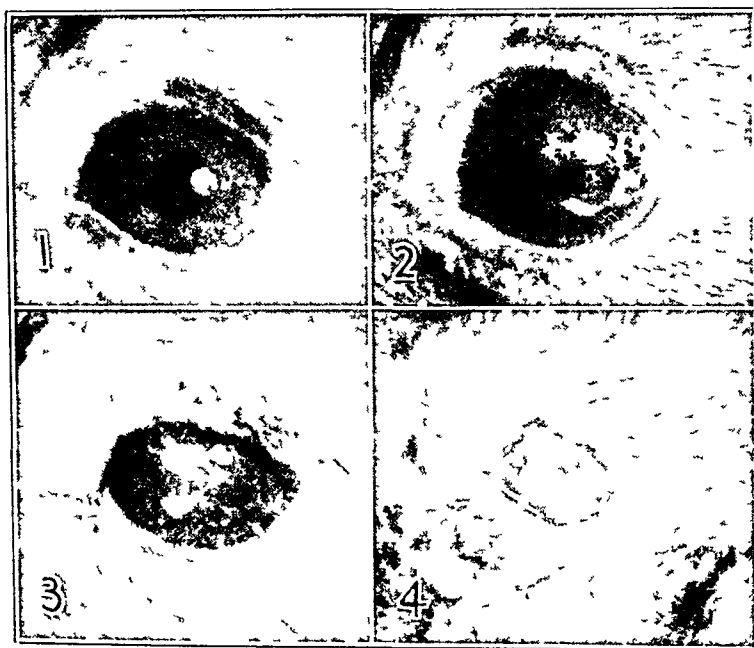


Fig 3—Primary ocular vaccinia in nonimmune rabbits thirty-one days after inoculation (experiment 1). 1 shows the best, and 3 the worst, results in group C (those treated with roentgen radiation at the height of the lesion—seven and eight days after inoculation), 2 shows the best, and 4 the worst, results in group D (untreated).

half, three and three and a half days after inoculation of the eye). In group G, consisting of 3 rabbits, the treatments were given at the same time, but to the flank rather than to the eye.

**Results** The reactions to secondary inoculation of the cornea were less severe and the residual corneal opacities were less dense than those which followed primary inoculation (experiment 1). Severer reactions occurred in the group which received roentgen therapy to the flank (group G) than in the group in which the eyes were directly irradiated (group F). The results would indicate that the effect of direct irradiation of the corneal lesion is greater than the systemic effect of irradiation of a distant primary site. Local irradiation seemed to have less effect on the lesions of the flank than on the ocular lesions.

*B Effect of Roentgen Therapy on Primary Vaccinia of the Cornea in Animals Receiving Secondary Inoculations of the Flank*—The corneas of 6 rabbits were inoculated with vaccinia virus, after seventy-two hours, when the earliest lesions were visible, the flanks of the animals were inoculated with fresh virus. Group H,

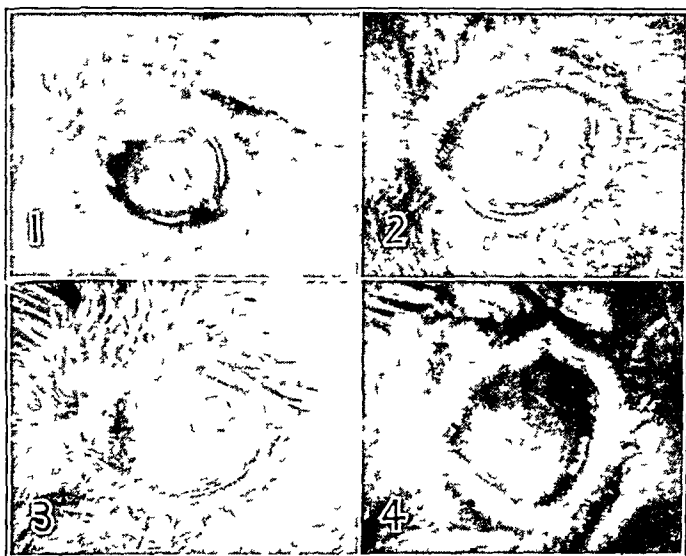


Fig 4—Effect of partial immunity on ocular vaccinia (experiment 2). The lesions shown are the severest in each of the four groups, thirteen days after ocular inoculation.

1 and 2 show the lesions of secondary ocular vaccinia. The eye in 1 (group F) was treated with roentgen radiation two and three days after inoculation of the eye and six and seven days after inoculation of the flank; the eye in 2 (group G) was treated at the same time, but with roentgen radiation to the flank rather than to the eye.

3 and 4 show the lesions of primary ocular vaccinia in animals receiving secondary inoculation of the flank seventy-two hours after inoculation of the eye. The eye in 3 (group H) was treated with roentgen radiation six days after inoculation of the eye; the eye in 4 (group I) was not treated.

consisting of 3 rabbits, received roentgen treatments to the eye one hundred and thirty-six, one hundred and forty-eight and one hundred and sixty hours after inoculation of the cornea. Group I, consisting of 3 rabbits, received no roentgen therapy and served as a control on the effect of immunity alone.

**Results** The lesions in the group which received roentgen therapy to the eye after secondary inoculation of the flank (group H) were comparable in severity to those in group F (secondary vaccinia of the cornea treated by local irradiation). The severest reaction observed in experiment 2 was that in an animal in group I, which received no roentgen therapy (fig 4). The acute lesions in the corneas of the irradiated animals subsided more rapidly than those in the nonirradiated ones.

Four animals in experiment 2 failed to show corneal lesions, though 1 of these had a conjunctival lesion. The 3 animals which failed to show ocular lesions were evenly distributed in groups F, H and I. The animals in experiment 2 were all slightly smaller and younger than those in experiment 1. The virus may have become attenuated during three weeks of storage between the two experiments, though it had not been removed from the refrigerator. That the virus was active is shown by the development of lesions on the flanks of all animals and by subsequent successful human inoculations. Difference in technic is a possible explanation of the failures in experiment 2, since the inoculations were done by a different member of the team and the scratches were sometimes slightly shorter than those in experiment 1. Partial immunity induced by inoculation of the skin may have been a greater factor than any of these. Because of the small size of the groups in which the failures occurred, the conclusions reached cannot be subjected to statistical analysis.

*Conclusions*—On the basis of the preliminary experiments, it was concluded that roentgen therapy for primary or secondary vaccinia infection of the eye hastens regression of the acute lesion and probably diminishes the residual corneal opacities. The optimum time for therapy appears to be between the appearance of the lesion and the time it reaches its height. Treatment very early, as soon as inoculation would be suspected, delays the appearance, but does not prevent the full development of the lesion.

#### ADDITIONAL EXPERIMENTS

The investigation was pursued further, with the number of variables reduced and the size of the individual groups increased. The corneal inoculations were done simultaneously in all groups to avoid possible attenuation of the virus. Measurements of the decrease in transmission of light were made within thirty minutes of the death of the animal.

*Experiment 3—Determination of the Relative Value of Roentgen Therapy and Partial Immunity in Corneal Vaccinia* *A Value of Roentgen Therapy in Primary Corneal Vaccinia*—In group J, consisting of 15 animals, the treatments were given one hundred and three, one hundred and twenty-seven and one hundred and forty-eight hours (four, five and six days) after inoculation. In group K, consisting of 15 rabbits, the animals received no radiation and served as positive controls on the effect of roentgen therapy. Group L, consisting of 5 rabbits, served as a control on the extent of damage done by trauma, irradiation and chemical irritation—negative control. Both eyes of each animal were anesthetized and scarified, only the right eye was irradiated.

*Results*—All animals in groups J and K showed inflammatory reactions of the corneas and bulbar conjunctivas, corneal opacities were noted in each. No visible lesions were seen in any animal in group L. The galvanometric readings of the photoelectric colorimeter (T) were subtracted from 100 to give the per cent of loss of transmission by light scattered and absorbed, these data are recorded in table 2. Since the decrease in transmission of light by the cornea of the right (irradiated) and that by the cornea of the left (nonirradiated) eyes in group L were almost identical, the data on both eyes are recorded to increase the size of the sample for statistical analysis.

*B Value of Roentgen Therapy and Partial Immunity in Secondary Vaccinia of the Cornea in Animals Partially Immune As a Result of Primary Inoculation of the Skin*—Thirty rabbits were inoculated on the flank with vaccinia virus three days before inoculation of the corneas. The corneas of groups J and K

(experiment 3A) and groups M, N and O were inoculated at the same time from the same lot of virus, so that results for the various groups could be more accurately compared. Group M, consisting of 15 rabbits, received roentgen treatments to the eye on the seventh, eighth and ninth days after inoculation of the flank (one hundred and three, one hundred and twenty-seven and one hundred and forty-eight hours after inoculation of the eye). Group N, consisting of 15 rabbits, received no radiation and served as a control on the effect of partial immunity alone. Group O, consisting of 15 rabbits, was inoculated on the flank three days after inoculation of the eye, but received no radiation therapy and served as a further control on the participation of the eye in immunity.<sup>5</sup>

TABLE 2—Decrease in Transmission of Light in Eyes with Primary Vaccinia Treated with Roentgen Radiation\*

Group	100—T† Filter 660			100—T Filter 540			100—T Filter 440		
	J *	K *	L *	J	K	L	J	K	L
1	4 75	5 50	1 75	7 00	10 25	4 00	16 00	46 00	6 50
2	47 75	2 75	1 25	60 00	4 00	3 00	13 00	18 00	7 00
3	2 50	3 75	0 75	5 00	6 00	2 50	20 00	8 00	11 25
4	6 50	23 75	1 75	10 00	32 00	3 50	7 00	6 00	
5	6 50	7 25	1 00	8 00	11 00	2 50	4 50	11 50	
6	5 25	0 50	1 50	11 25	3 75	3 75	6 50	10 50	
7	3 00	1 75	1 50	3 50	3 25	3 50	19 50	14 50	
8	0 75	3 50	0 75	1 50	6 50	3 50	9 50	8 00	
9	1 50	4 25	1 25	3 25	6 50	2 50	6 50	10 00	
10	8 50	5 00	0 75	13 00	8 00	2 75	8 00	12 00	
11	3 25	3 75		5 25	4 50		10 50	9 00	
12	2 25	4 25		3 50	6 00		7 50	6 00	
13	2 75	5 50		4 50	7 50				
14	4 50	3 50		6 25	5 25				
15	4 00	1 00		5 00	2 25				
Mean	6 91	5 06	1 22	9 80	7 78	3 15	10 70	13 29	8 25
N	15	15	10	15	15	10	12	12	3
σ	11 485	5 462	0 339	14 200	7 130	0 568	5 255	10 862	2 13

\* Group J was not treated (positive control), group K was treated, group L was not inoculated (negative control)  
 † T represents the galvanometric readings of the photoelectric colorimeter

Results All animals in groups M, N and O showed inflammatory reactions of the corneas and bulbar conjunctivas. Corneal opacities were not present in 2 animals of group M and in 3 animals of group N, on the sixteenth day, 2 animals of group O showed no corneal opacities, and the corneas of 4 additional animals cleared, so that no visible lesions were present in 6 rabbits at the time the animals were killed.

5 Groups P and Q, on which data are given in the paper describing a photoelectric method for measurement of transmission of light, will not be further considered here.<sup>2</sup> The data designated as group P represent readings on the untraumatized and uninoculated cornea of rabbits with ocular vaccinia selected at random from groups J, K, M, N and O. These data indicate the degree of impairment of transmission of light by possible spread of the infection by natural routes to the opposite eye of the animal. Group Q consisted of 5 normal rabbits.

Pustules did not develop in the flanks of 10 animals in group M, only 5 animals which had evidence of severe infection of the flank survived for the duration of the experiment, hence, this group was quite small. Only 1 animal in group N failed to have a take on the flank, this animal had a grossly infected left (uninoculated) eye. All animals in group O had satisfactory takes on the flank.

Four animals in group M died after the fourteenth day of inoculation of the eye, and before they were killed, 1 animal in group N died on the day after inoculation of the eye. The animal from group N showed bilateral abscesses of the lung with empyema at autopsy, no apparent cause of death was observed in the others.

TABLE 3—*Decrease in Transmission of Light in Eyes with Secondary Vaccinia Treated with Roentgen Radiation\**

Group	100—T Filter 660			100—T Filter 540			100—T Filter 440		
	M *	N *	O *	M	N	O	M	N	O
1	3.75	1.50	3.25	6.00	3.50	5.50	11.00	6.00	14.00
2		1.00	6.75	3.00	3.50	9.75	11.50	6.00	26.50
3	2.75	2.00	2.00	4.25	3.75	4.25	7.50	11.00	7.00
4	8.75	1.75	3.00	12.25	3.50	5.25	20.00	7.00	8.50
5	6.75	1.50	13.75	10.75	5.50	18.00		4.50	17.00
6	4.50†	1.25	0.75	6.25†	3.00	3.25	30.50†	32.00	24.00
7	3.00†	0	3.00	5.50†	1.50	3.50	7.00†	6.00	6.00
8	63.25†	9.75	7.50	75.50†	13.75	10.00	7.00†	39.50	7.00
9	13.75†	2.00	11.25	19.50†	3.00	16.00		8.00	4.50
10	0.50†	21.75	2.50	3.75†	29.00	4.00		8.00	14.00
11	3.25†	2.50	2.00	3.50†	4.25	3.75		8.00	9.00
12		3.75	1.25		4.75	2.50			10.00
13		2.75	6.00		4.25	8.75			
14			3.50			5.50			
15			3.50			6.00			
Mean	5.50 (10.97)	3.92	4.66	7.25 (13.65)	6.40	7.06	12.50 (13.50)	12.36	12.27
Number	4 (10)	13	15	5 (11)	13	15	4 (7)	11	12
σ	2.39 (18.739)	5.846	3.744	3.62 (21.101)	7.399	4.656	4.59 (8.775)	11.802	7.095

\* Group M was treated, group N was not treated (immune control), group O was not treated and received inoculation of flank after inoculation of eye.

† These animals did not get pustular takes on the flanks, the calculations within parentheses ( ) include these data.

The degree of impairment in transmission of light is recorded in table 3.

*Statistical Analysis*—The comparison of the effect of roentgen therapy and immunity on the transmission of light is given in table 4. The values for *t* was calculated by "Student's" method.<sup>4</sup> The impairment of transmission of light as determined by the photoelectric technic apparently was not significantly altered by either roentgen therapy or immunity or by a combination of the two. Though the number of animals in group M was reduced by the failure of pustules to develop in all after inoculation of the flank, the interpretation of the statistical analysis was not altered by recalculation of the data after the inclusion of animals without pustular takes.

#### COMMENT

The experiments do not clearly demonstrate that either immunity or roentgen therapy protects the eye against permanent damage by vaccinia infection. Opti-

TABLE 4—Statistical Comparison of Effects of Roentgen Therapy and Immunity on Transmission of Light \*

Groups Compared	Effect of roentgen therapy on primary immunity	Filter 660			Filter 540			Filter 440			Interpretation	
		n	Calculated t	Significant Level (5%) t	Interpretation	n	Calculated t	Significant Level (5%) t	Interpretation	n		Calculated t
K and I	Effect of roentgen therapy on primary immunity	28	0.564	2.048	Not Significant	28	0.492	2.048	22	0.925	2.074	Not Significant
M and N	Effect of roentgen therapy on secondary immunity	15 (21)	0.5146 (1.28)	2.131 (2.080)	Not Significant	16 (22)	0.2417 (1.62)	2.120 (2.074)	13 (16)	0.0225 (0.219)	2.160 (2.120)	Not Significant
M and J	Effect of immunity on roentgen therapy	17 (21)	0.2389 (0.607)	2.110 (2.080)	Not Significant	18 (24)	0.2370 (0.554)	2.101 (2.064)	14 (17)	0.2777 (1.075)	2.145 (2.110)	Not Significant
M and K	Effect of immunity plus roentgen therapy	17 (23)	0.1619 (1.161)	2.110 (2.069)	Not Significant	18 (24)	0.1616 (1.009)	2.101 (2.064)	14 (17)	0.1241 (0.043)	2.145 (2.110)	Not Significant
K and N	Effect of partial immunity	13	0.532	2.056	Not Significant	13	0.502	2.056	11	0.197	2.080	Not Significant
O and K	Effect of secondary inoculation of the flank	28	0.234	2.048	Not Significant	28	0.326	2.048	22	0.272	2.074	Not Significant
O and N	Participation of the eye in immunity	26	0.408	2.056	Not Significant	26	0.286	2.056	21	0.022	2.080	Not Significant

\* The figures in parenthesis were obtained by including data on animals in group M which did not get a tube on the flank

imum conditions to insure infection were met, the inoculum was large, diet, vitamin and fluid intakes were maintained, and the possibility of pseudoestrus was avoided<sup>1</sup>

*Value of Roentgen Therapy*—Roentgen therapy appeared to be of value in the treatment of acute lesions of ocular vaccinia, as judged by clinical observation. The clinical impression that roentgen therapy may be valuable in decreasing residual corneal opacities was not borne out by experiments on the transmission of light, utilizing a photoelectric technic. Roentgen therapy would appear to have the same value in the treatment of secondary as of primary vaccinia, immunity did not appear to enhance the value of roentgen therapy for either acute or chronic lesions. The values for the means of the decrease in transmission of light might suggest that roentgen therapy was harmful, this is not borne out by the statistical comparison. The differences in transmission between the corneas of uninfected but traumatized animals which were irradiated and corneas which were not irradiated (right and left eyes of group L) and between the corneas of groups J and K and the corneas of groups M and N were so small that it was concluded that roentgen therapy was not harmful and did not increase corneal opacities.

*Role of Immunity in Ocular Vaccinia*—Clinical observation on patients and experimental animals has convinced us that partial immunity protects against residual corneal opacities. If the mean of the decrease in transmission of light in group M as calculated with the animals included in which pustular takes of the flank did not occur is compared with the mean calculated with these animals excluded, it is evident that the decrease was less in the animals which should have partial immunity from the pustular take. The fact that takes were obtained on the flank of the animals of group O after inoculation of the eye and that takes were obtained in the eye of the rabbits of group N after inoculation of the flank could be interpreted to indicate that the eye does not participate in immunity. Cellular immunity may develop in the eye, but more slowly than in the skin, and a sufficient interval may not have elapsed after inoculation of the flank for the eye to have become partially immune, the experiments reported cannot answer this question.

On the basis of the results in group O, secondary inoculation of the arm in a human being with ocular vaccinia may be of no value but would appear to do no harm.

The lack of statistical significance in the comparison of group M with other groups, whether calculated to include or to exclude the animals without pustular takes on the flank, could be interpreted to indicate that partial immunity prevents little damage which leads to decrease in transmission of light. These data could also be interpreted to indicate that a low degree of immunity, resulting from a presumptive take in the flank, which showed edema and erythema but no pustules, affords the same protection as a violent local take.

*Critique of the Photoelectric Technic*—The decrease in transmission of light objectively measured by the photoelectric technic agreed well with the clinical estimate in moderate and severe degrees of corneal opacity. The technic was of definite value in the detection of minimal lesions. In several instances, opacities which had been overlooked during life were found to be barely visible to the unaided eye on careful reexamination of the excised cornea after a decrease in transmission was observed by the photoelectric technic. The detection of minimal lesions probably explains the variation in interpretation of results in the preliminary qualitative and in the additional quantitative experiments. Subclinical



lesions, however, would be of little clinical importance, and probably would result in some loss of color vision only, as discussed later

The photoelectric technic appears to measure the amount of light transmitted, nontransmitted light includes that scattered, which varies with the wavelength of the filter used, as well as that absorbed.<sup>2</sup> The opacities, which appear to act as neutral absorbing filters at all wavelengths, were not homogeneous and were not uniformly distributed over the area of cornea involved. The colorimeter is designed for the measurement of transmission through a homogeneous solution, when a filter is used, measurements are made at a single wavelength. The photoelectric technic as used is not ideal for such experiments, since a method which measures transmission cannot be applied to patients or to intact animals. We have not been able to devise a better method, however.

The use of types of therapy other than are evaluated here are discussed elsewhere.<sup>1</sup>

### SUMMARY

Roentgen therapy appeared to be of value in the treatment of acute lesions of ocular vaccinia in experimental animals. The clinical impression that roentgen therapy was of value in decreasing residual corneal opacities was not borne out by measurements of the transmission of light with a photoelectric technic.

Partial immunity of the eye, resulting from previous inoculation of the skin, appeared on the basis of simple observation of experimental animals to decrease the residual corneal opacity of ocular vaccinia. This impression was not confirmed by a statistical comparison of the decrease in transmission of light through the excised cornea of nonimmune and partially immune rabbits, as measured by a photoelectric technic.

The discrepancy between simple observation and statistical comparison of the objective measurements may be due to the detection of minimal or subclinical lesions by the photoelectric technic and to the range in individual variation of the experimental animals.

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# DISTANCE DISCRIMINATION

## III Effect of Rod Width on Threshold

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THE USUAL form of the rod test for distance discrimination has been designed to exclude all cues of distance except retinal disparity. In spite of this intention, the size cue has not been eliminated. In the Howard test, widely used in the armed forces and in industry, the size cue acts in harmony with, and supplements, retinal disparity. In other tests, of which the "telebinocular" may be taken as an example, size becomes not a secondary, but a confusion, factor. With the "telebinocular" judgments based on retinal disparity are scored as correct responses, while size of the objects enters only to confound the observer. In a normal situation an object looks larger as it approaches the eye, in the "telebinocular" the smallest letter may be, on the basis of binocular parallax, the nearest. This pitting of the size cue against the disparity cue is also a feature of the Verhoeff "stereoptor," in which the subject must judge the relative distances of three objects of different sizes. The intent in these tests obviously is to eliminate size as a basis of judgment. Instructions to disregard size, equally obviously, cannot prevent size from influencing judgment. For these, and other, reasons it is desirable to know the effect of size on binocular distance discrimination.

### EXPERIMENT 1

*Methods*—The general features of the apparatus have been described in a previous paper<sup>1</sup>. The subject, seated at a distance of 10 meters from the position of instrumental equality, observed the two rods through an aperture 17.5 by 32.5

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1 Weymouth, F. W., and Hirsch, M. J. The Reliability of Certain Tests for Determining Distance Discrimination, *Am J Psychol* 58 379-390, 1945

cm The rod on his left was stationary and served as a standard of distance The rod on the right was movable toward or away from the subject by a motor which he started or stopped with a switch, the direction of movement was controlled by the experimenter Four test conditions were used, in each of which the right, or movable, rod had a diameter of 2 cm, the left, or standard, rod measured 1, 2, 3 and 4 cm in conditions *A*, *B*, *C* and *D*, respectively For all four conditions the inner edges of the rods were separated by 5 cm

The subjects were 7 university students Each subject made observations on three days, the first set of observations was considered practice, the second and third sets were recorded and constitute the data presented here There were rest periods, and no day's observations covered more than one hour In all, 30 observations were made for each of the four conditions—15 observations for each condition on the second day and 15 observations on the third day The order of presentation of the conditions was not the same for all observers, nor was it the same for any subject on different days

The subject looked away from the aperture between observation while the experimenter set the movable rod approximately 300 mm nearer or farther than the standard This distance proved in all cases to be above the threshold At a signal from the experimenter, the subject looked at the rods, answered "near" or "far" and threw the switch setting the rod in motion The movable rod approached the standard, and when the rods appeared equidistant, the subject stopped the motor and looked away The direction and distance, expressed in millimeters, of the movable rod from the standard were recorded, and the procedure was repeated

*Results*—The conditions of the experiment gave groups of 15 observations for each subject, two directions of movement and four widths of standard rod, making a total of 840 observations Each group of estimates of equal distance obtained with this form of the average error method gives a distribution which may be characterized by two statistical measures, the mean and the standard deviation The mean represents the best estimate of the subject as to the position of equality of the movable and the comparison rod, or position of subjective equality ( $E_s$ ), the standard deviation ( $S_x$ ) represents the variability of the settings and has been adopted as the threshold, following Boring (The psychophysics of distance discrimination is discussed in the first paper of this series<sup>2</sup>) This threshold is equivalent to the distance from the mean ( $E_s$ ) to a point cutting off the extreme 16 per cent of the measures

The mean and the standard deviation for all these groups were calculated Differences due to the direction of approach proved not to be statistically significant, and the two sets were combined The means, or positions of subjective equality, are presented in table 1, the standard deviations, or thresholds, in table 2 Considered as standard deviations, the latter are homogeneous, since by Bartlett's test a *P* of 0.125 was obtained Treated as thresholds by analysis of variance, they showed no

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<sup>2</sup> Hirsch, M. J., and Weymouth, F. W. Distance Discrimination I Theoretic Considerations, *Arch Ophth* 39:210 (Feb) 1948

significant differences. On the basis of the average threshold, the angle of binocular disparity amounted to 7.72 seconds. The means, on the other hand, showed significant differences for observers, conditions and interaction when compared with the intraobservation variance. When the more rigorous criterion of the interaction of observer and conditions was used, the variance associated with conditions gave a significant ratio ( $P = 0.01$ ). Thus, it is clear that in spite of the differences in reaction of subjects to the different widths of rods, the conditions exert a significant effect on the position of subjective equality.

TABLE 1—*Position of Subjective Equality for Each Condition*

Condition	A	B	C	D
Left rod size, cm	1	2	3	4
Right rod size, cm	2	2	2	2
Subject	Position of Subjective Equality ( $E_s$ ), Mm			
A	-3.03	-45.77	-66.57	-27.73
B	-47.43	+1.63	-21.40	-45.40
C	-13.93	-29.93	-29.67	-31.93
G	+46.07	+43.63	+16.30	+7.57
L	-8.03	-22.13	-32.83	-40.23
M	+10.10	+40.83	-42.27	-77.63
O	+43.50	+9.97	-22.97	-26.77
Average	+3.89	-0.25	-28.49	-34.59

TABLE 2—*Standard Deviation for Each Condition*

Condition	A	B	C	D
Left rod size, cm	1	2	3	4
Right rod size, cm	2	2	2	2
Subject	Position of Subjective Equality ( $E_s$ ), Mm			
A	68.13	73.33	76.54	86.81
B	102.32	67.86	70.18	119.93
C	33.89	39.28	47.18	44.69
G	75.13	52.21	62.30	45.31
L	31.21	44.71	33.99	33.37
M	57.56	61.55	45.86	47.24
O	47.52	52.71	48.30	42.60
Average	59.39	55.95	54.91	59.99

The values for  $E_s$  differed significantly. It will be noticed that the 2 cm right (movable) rod was set farther than instrumental zero when the fixed rod was smaller, but was set progressively nearer as the width of the fixed rod increased. The data give a linear regression which is significantly different from zero, but for four points it is not safe to try to fix the exact form of the function, all that can be said is that the threshold is a significantly increasing function of rod width. This is what might have been expected, the right rod, when smaller, is placed nearer the observer, a position tending to equalize the visual angles of the two rods.

## EXPERIMENT 2

In the preceding experiment the effect of size on the position of subjective equality and the standard deviation ( $E_s$  and  $S_x$ ) was determined. The statistical technic involved was an analysis of variance. The present experiment differed only slightly and affords the possibility of checking the effect of size cue on  $E_s$  for single observers.

**Methods**—Through an opening 10 by 23 cm in the partition, two rods were seen against a background of opal glass, transilluminated at a level of 25 millilamberts. The subject, seated 127 meters from instrumental zero (the passing point of the rods) and 8 meters from the partition, controlled the motion of the motor-driven movable rod with a switch. At instrumental zero the rods were separated laterally by a distance of 6 cm, corresponding to an angle of 163 minutes. The diameters of the rods for the three conditions were

- (a) Both rods, 1 cm (visual angle, 2 7')
- (b) Right rod, 2 cm (visual angle, 5 4')  
Left rod, 1 cm (visual angle, 2 7')
- (c) Right rod, 1 cm (visual angle, 2 7')  
Left rod 2 cm (visual angle, 5 4')

The position of the right (movable) rod at the beginning of each trial was approximately 20 cm from instrumental zero, behind the comparison rod for half the trials and in front of it for the other half. For each of the three conditions, 30 trials were run after a short series of practice trials. The deviation from instrumental zero for each trial was recorded, as plus (+) if the movable rod was set behind the stationary rod and as minus (—) if it was set in front. The 30 trials for each of the three conditions were presented in groups of five, so that any practice effect which had not been eliminated by the practice series would be divided among the three conditions. Five students, 4 sophomores and 1 graduate student, served as observers.

**Results**—The mean (position of subjective equality) and the standard deviation (threshold) were calculated for each observer and

TABLE 3—Mean ( $E_s$ ) and Standard Deviation ( $S_x$ ) for Five Observers for Three Conditions

Observer	Position of Subjective Equality ( $E_s$ ), Mm			Threshold ( $S_x$ )		
	Rods of Equal Size	Right Rod Larger	Left Rod Larger	Rods of Equal Size	Right Rod Larger	Left Rod Larger
1	+19 233	+19 033	+ 1 433	33 843	32 372	25 969
2	+ 1 567	+72 933	—25 000	65 976	50 955	67 782
3	— 3 475	+12 100	—22 925	50 638	48 704	66 017
4	+ 4 400	+22 700	—29 767	25 844	23 851	31 788
5	+ 6 700	+42 200	— 9 000	33 799	35 426	42 920
Average	+ 5 635	+33 793	—17 052	42 020	38 262	46 896

for each condition, these data are presented in table 3. When the analysis of variance was applied, results similar to those of the first experiment were obtained. The threshold showed no significant differences in the conditions ( $P=0.20$ ), the positions of subjective

equality, in contrast, were significantly different ( $P = 0.001$ ). In addition, the differences in  $E_s$  for individual subjects were tested for significance, as may be seen from table 4, subject 1 showed a  $P$  of 0.02—values for all others were less than 0.01.

The displacement of the  $E_s$  was in all cases in harmony with the results of the first experiment, the movable rod, if smaller, was set closer to the observer, if larger, farther, there being in each trial a tendency to equalize the visual angles of the two rods.

#### COMMENT

The two experiments, although carried out at different times with different observers, gave results agreeing in all essential features. A relatively simple sensory situation was presented, in which distance perception must rest chiefly or exclusively on two clues, retinal disparity and image size. The task is to set a movable rod at the same distance

TABLE 4—*Differences Between Positions of Subjective Equality (Mean) for Right Rod Larger and for Left Rod Larger*

Subject	Difference in ( $L_s$ ), Mm	P
1	17.600	0.0203
2	97.933	<0.0001
3	85.025	0.0069
4	52.467	<0.0001
5	51.200	<0.0001
Average	50.845	

as the standard rod, and the significant variable is the relative sizes of the rods. The measures are the mean of the settings, or position of subjective equality,  $E_s$ , and the standard deviation of the distribution, which is here used as the threshold.

It was found that the threshold shows no significant over-all variability with changes in the size of rods. Although, in the first experiment, with four widths, the situations with the greatest difference in rod size showed larger thresholds, these reached only the 2 per cent level, and could merely be considered suggestive.

In contrast, the position of subjective equality varied significantly with the width of the rod. When the stationary reference rod was wider than the movable rod, the latter was stopped nearer the observer, a sort of "constancy" response in which an attempt is made to equalize the visual angles of the rods in spite of the known difference in size. Although the displacement of  $E_s$  increased with the difference in the size of the rods, giving a significant regression, the form of the regression cannot be determined from so small a series of widths.

Although significant, and in the direction reasonably to be expected, these displacements are extremely small. The terms in which they

should be presented and the perceptual mechanism leading to such minute displacements require consideration. Table 5 is an attempt to present the data on  $E_s$  in a readily understood form. The first three columns identify the conditions and give the widths of the rods. Column 4 gives the positions of subjective equality. Column 5 gives the position of subjective equality ( $E_s$ ) referred to the position of subjective equality with rods of equal width. Column 6 gives the value of column 5 as a per cent of the displacement necessary to make the angular sizes of the rods the same, column 7 gives the value of column 5 as a per cent of the average threshold for that experiment. Column 8 gives the difference in angular size resulting from a displacement of the movable rod equal to the value of column 5.

It will be seen that in terms of the displacement required to give equality of angular size, the  $E_s$  is negligible, not reaching 1 per cent.

TABLE 5—*Analysis of Changes in the Position of Subjective Equality ( $E_s$ )*

1	2	3	4	5	6	7	8
	Width Fixed Rod, Cm	Width Movable Rod, Cm	$E_s$ Cm	$E_s - E_e$ Cm	$\frac{100 E_s}{D_e}$ %	$\frac{100 E_s}{Th}$ %	Size Difference Sec
A	1	2	+0.389	+0.415	+0.04	+7.2	+0.34
B	2	2	-0.025	0.000			
C	3	2	-2.849	-2.823	-0.65	-49.0	-1.16
D	4	2	-3.459	-3.434	-0.47	-59.7	-1.42
a	1	1	+0.568	0.000			
b	1	2	+3.379	+2.811	+0.22	+66.3	+0.72
c	2	1	-1.705	-2.274	-0.36	-53.6	-0.29

Column 5 Difference between the  $E_s$  obtained for the condition and the  $E_e$  obtained with rods of equal size ( $E_e$ ).

Column 6 Value of column 5 as a per cent of the total distance required to give equal angular size to the rods.

Column 7 Value of column 5 as a per cent of the average threshold for corresponding condition.

Column 8 Change in angular size of the rod (expressed in seconds of arc) when displaced by the value of column 5.

The difference in angular size corresponding to  $E_s$  is, likewise, surprisingly small, in no case equaling 2 seconds, although the corresponding retinal disparities are 7.7 and 3.5 seconds. Perhaps the most significant comparison is with the average threshold for the same experiment. Here, the values range from 7 to 66 per cent.

Although the sensory situation appears to be relatively simple, namely, a pattern consisting of two cues—retinal disparity and angular size in congruent and incongruent relations—the perceptual analysis is not easy. The response is clearly dominated by retinal disparity. The size cue, in the situations in which the rods differ in size, and therefore in which there is an apparent incongruence between the two cues, appears to produce a displacement tending to equalize the visual angles.

of the rods. This seems little more than a "token" displacement, but the direction is in all cases consistent, and the greater the difference in size of the rods, the greater the displacement. The maximum displacement is 66 per cent of the threshold, and it will be remembered that the threshold is the standard deviation of the distribution of equality settings. Measured from the mean of this distribution, that is, from the position of subjective equality with rods of equal width, this displacement, or deviation, would include nearly one quarter of the cases. Pitted against the stronger cue of retinal disparity, the size cue may shift the  $E_s$  within the original distribution, but seems incapable of displacing the point into a region contradicting the reports of retinal disparity. Of course, it will be obvious that before equality of angular size is actually realized, retinal disparity will have indicated not only "near" or "far" but "double," and the size cue seems unable to override disparity.

There are still practical consequences to be considered. The introduction of the size cue incongruent with the parallax, or disparity, cue has a significant effect on the position of subjective equality but does not significantly affect the threshold. As pointed out in an earlier paper of this series,<sup>2</sup> the  $E_s$  is a useful measure of aniseikonia. Experiments with size lenses which support this view will be presented in a subsequent paper.<sup>3</sup> For the present, however, it is sufficient to point out that any testing instrument or method which includes the size cue in a manner incongruent with the parallax cue cannot yield a meaningful  $E_s$ , and since this parameter is a measure of aniseikonia, such a method cannot yield any information about aniseikonia. While such instruments as the "telebinocular" and the "stereopter" give thresholds, it is difficult to state just what is being measured.

In the Howard test the size cue is present, but in a normal, or congruent, fashion. Experiments in this laboratory have shown that under these conditions the resulting position of subjective equality and the threshold are normal. Thus, if both these measures are calculated, information on aniseikonia is obtained, a result not possible with the two tests mentioned.

#### SUMMARY

With apparatus similar to the Howard test but with rods of different widths, the effect of incongruence between binocular parallax and size on distance discrimination was studied.

The threshold or variability of settings of equality was not significantly affected.

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<sup>3</sup> Hirsch, M. J., Horowitz, M. W., Walker, E. L., and Weymouth, F. W. Distance Discrimination. IV. Effect of Aniseikonic Lenses, *Arch. Ophth.*, this issue, p. 333.



The position of subjective equality was significantly affected, the position of subjective equality ( $E_s$ ) being shifted in the direction of size equality to an increasing degree by increasing the difference of width

The possible perceptual interpretation of this displacement is discussed

In other papers of this series it has been pointed out that the position of subjective equality is of value as a measure of aniseikonia. Therefore, any test that introduces size as a confusion factor with the intention of "eliminating size" distorts the results ascribed to binocular parallax, renders the test inaccurate and makes it impossible to obtain information on aniseikonia.

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## DISTANCE DISCRIMINATION

### IV Effect of Aniseikonic Lenses on Distance Discrimination

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IN THE first paper of this series on distance discrimination<sup>1</sup> it was shown that the results obtained in a test of depth perception might be made to yield two important types of information. If a series of judgments are made, the mean of the distribution expressed in physical units (customarily millimeters) is the position of subjective equality ( $E_s$ ), and from it may be determined the location of pairs of functionally corresponding retinal points. The standard deviation of the distribution ( $S_x$ ) may be used to determine the size and relative sensitivity of the pair of corresponding areas. It was pointed out in the paper just mentioned that tests (such as the Howard) which are used today to test distance discrimination are scored in a manner which yields a single measure rather than the two parameters,  $E_s$  and  $S_x$ . This single measure, while enabling the comparison of members of a group of observers to be made, entails the loss of considerable information. In the third paper of this series,<sup>2</sup> it was pointed out that such tests as the "telebinocular" or the Verhoeff "stereoptor" method not only yield a single measure but, unlike the Howard, cannot be used to give two measures even if the experimenter wished to do so.

The aim of the present experiment was to determine the effect of size lenses on the position of subjective equality ( $E_s$ ) and the stand-

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1 Hirsch, M J, and Weymouth, F W Distance Discrimination I Theoretic Considerations, Arch Ophth, to be published

2 Hirsch, M J, Horowitz, M W, and Weymouth, F W Distance Discrimination III Effect of Rod Width on Threshold, Arch Ophth, this issue, p 325

ard deviation of the distribution ( $S_x$ ) Three lenses representing 1, 2 and 3 per cent over-all magnification were used<sup>3</sup>

# METHODS

The variable rod apparatus, formerly described,<sup>4</sup> was used with the angular size of the movable rod constant, thereby eliminating the size cue. The rods were observed at 10 meters, at which distance they were 25 cm wide and were separated by 10 cm. The central portions of the rods were seen through an aperture as a black silhouette against a transilluminated milk glass screen. The experimenter set the right (movable) rod initially at a position noticeably near or far, the subject, who controlled its motion by a switch, set the movable rod equidistant with the standard. The subject was not aware of which lens he was wearing, since the experimenter made the changes in the lens, nor did he know before which eye the size lens was placed, since a plano lens was placed before the eye not having the magnification lens.

Seven conditions of observation were given with the use of a lens of 1, 2 or 3 per cent magnification before either eye combined with a plano lens before

TABLE 1—*Positions of Subjective Equality ( $E_s$ ) for Four Subjects for Seven Different Combinations of Size Lenses\**

Subject	R <sub>3</sub>	R <sub>2</sub>	R <sub>1</sub>	O	L <sub>1</sub>	L <sub>2</sub>	L <sub>3</sub>
1	-415.98	-273.72	-192.12	-68.19	-16.17	+50.59	+161.40
2	-119.79	-107.79	-72.98	+31.00	+99.83	+200.87	+173.44
3	-368.81	-284.81	-223.83	-128.48	-16.96	+10.85	+17.98
4	-178.21	-102.54	-33.02	+30.17	+126.50	+185.94	+262.15
Average	-270.70	-192.22	-130.49	-33.88	+48.30	+112.09	+153.74

\* The values of position of subjective equality are expressed in millimeters

the fellow eye, and of plano lenses before both eyes. The conditions are indicated by the symbols R<sub>3</sub>, R<sub>2</sub>, R<sub>1</sub>, O, L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub>. The symbols R and L indicate the eye before which the size lens was placed, the subscript, the per cent of magnification. For each of these seven conditions there were 48 judgments of equality. The mean and the standard deviation (hereafter called threshold) for each of the sets were computed. In all, measurements were made on 4 trained observers. The thresholds are expressed in millimeters, the negative sign indicating that the movable (right) rod was set nearer, and the positive sign, that it was set farther, than the standard.

# RESULTS AND COMMENT

The positions of subjective equality and the thresholds, expressed in millimeters, for each observer and for each of the seven conditions, together with averages, are shown in tables 1 and 2. The standard deviations were combined in two different ways, the average threshold

3 The Vision Laboratory received from Prof. Kenneth B. Stoddard, University of California School of Optometry, the three aniseikonic size lenses used in this experiment.

4 Weymouth, F. W., and Hirsch, M. J. The Reliability of Certain Tests for Determining Distance Discrimination, *Am. J. Psychol.* 58:379-390, 1945.

is the arithmetical mean of the four standard deviations, while the combined threshold is the standard deviation for the 192 observations (48 observations made by each of the 4 subjects)

The effect of the lenses on the position of subjective equality was, in general, what might be expected. The magnitude of the  $E_s$  which should have resulted from each of the lenses can be calculated. A lens of 3 per cent magnification should displace the  $E_s$  291 mm at 10 meters, a lens of 2 per cent magnification, 195 mm, and a lens of 1 per cent magnification, 99 mm. For the 4 observers, whose average  $E_s$  with no lens was  $-33.88$  mm, resetting the origin to this point yields expected values for the  $E_s$  for each of the lenses as follows

$R_s$	$R_2$	$R_1$	$O$	$L_1$	$L_2$	$L_3$
$-324.88$	$-229.88$	$-132.88$	$-33.88$	$+65.12$	$+162.12$	$+257.12$

These calculated values for the  $E_s$  and the observed average for 4 observers are presented in figure 1. It will be seen that in each case

TABLE 2—*Thresholds ( $S_x$ ) for Four Subjects for Seven Different Combinations of Size Lenses\**

Subject	$R_3$	$R_2$	$R_1$	$O$	$L_1$	$L_2$	$L_3$
1	65.77	64.13	59.36	62.66	68.90	69.21	91.62
2	152.29	93.19	83.51	103.08	87.41	88.93	208.14
3	99.83	83.16	57.89	61.13	68.51	93.05	128.04
4	79.78	67.48	88.06	58.67	69.99	77.29	123.48
Average	99.17	78.24	72.21	71.38	73.70	82.12	137.82
Combined	162.57	117.91	108.42	100.21	98.97	117.08	168.81

\* Thresholds are expressed in millimeters

the values for the  $E_s$  lie between the position calculated from the effect of the size lenses and zero, the position of instrumental equality ( $E_i$ ). This trend of  $E_s$  can be fitted by a straight line, the slope of which differs significantly from the calculated values. There is a suggestion that the  $E_s$  deviates more from the calculated values with the stronger lenses at either end of the figure, but this is not statistically significant.

The reason for the systematic trend of the  $E_s$  toward instrumental zero is probably the presence of some factor other than binocular parallax. Burian<sup>5</sup> described the effect of wearing size lenses for a considerable time (eight to fourteen days). He concluded

The disparity factors can be largely disregarded when abundant perspective factors are present in a person's surroundings, but they become immediately operative when the perspective factors are scanty. Some persons with normal binocular vision are more apt to let the unocular factors influence the spatial localization derived from disparity clues than others, in whom the disparity clues dominate.

5 Burian, H. M. Influence of Prolonged Wearing of Meridional Size Lenses on Spatial Localization, *Arch. Ophth.* **30**: 645-666 (Nov.) 1943.

Since the disparity clue can be disregarded or judgments can be influenced by other cues, it is likely that some factor other than parallax was present and that this was responsible for the trend toward the position of instrumental equality ( $E_1$ )

The nature of the factor other than disparity is not clear. Monocular thresholds could not be obtained with the present method, the size cue usually encountered in the rod type of apparatus was eliminated by the gradually changing width of the rod, so that angular size was constant, other monocular cues were eliminated, as they are in all rod tests. It seems most likely that the factor was not one of the cues of distance discrimination, but was the more general time error

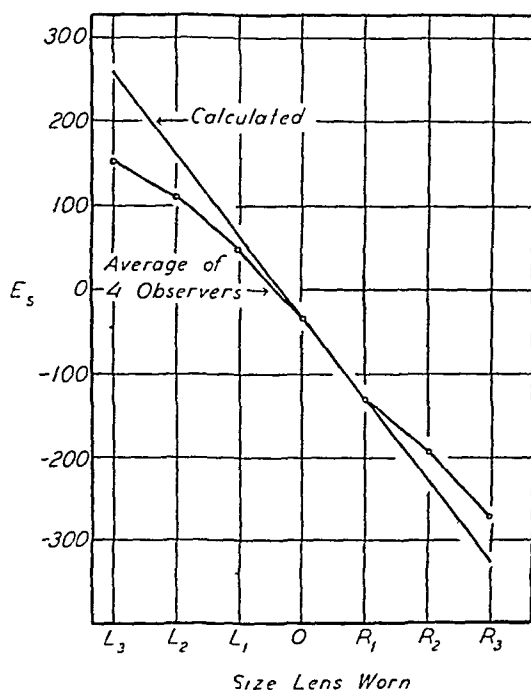


Fig 1—Effect of size lenses on the position of subjective equality ( $E_s$ )

It was stated earlier that for each judgment the rod was set perceptibly near or far and that the subject's task was to set the rod equidistant with the standard. However, for all lenses the distance was the same. Thus, with the plano lens the time required by the movable rod to reach  $E_1$  was of the order of ten seconds, whether it began at the noticeably near or at the noticeably far position. When the  $E_s$  was close to the  $E_1$ , the time had no effect. When, however, as in the case of the lens of 3 per cent magnification, the  $E_s$  was at some distance from the  $E_1$ , approximately five seconds was required to reach instrumental zero from one of the initial positions and fifteen seconds from the other. The tendency would be to overrun in the first case and to underrun in the second, both of which would bring the  $E_s$  closer to the  $E_1$ .

The average and combined thresholds ( $S_x$ ) presented in table 2 are shown in figure 2. In general, whether one considers the combined or the average threshold, the standard deviation is lowest for the plano lens or for the 1 per cent lens before either eye and is highest for the 3 per cent lens before either eye. As might be expected, the combined  $S_x$ , which includes the variability due to individual differences, is considerably higher for any lens than is the average  $S_x$ . The variance ratio of the  $S_x$  for either  $L_3$  or  $R_3$  and the  $S_x$  for no lens is significantly different to 1 in 1,000. That is, the combined  $S_x$  for either of the 3 per cent lenses is significantly higher than the  $S_x$  for the plano lens. Analysis of other data accumulated at the Vision Laboratory has yielded a low, but significant, positive correlation between  $E_s$  and  $S_x$ . The results just described are further evidence of this, the lenses which increase the magnitude of the  $E_s$  also increase the magnitude of the  $S_x$ .

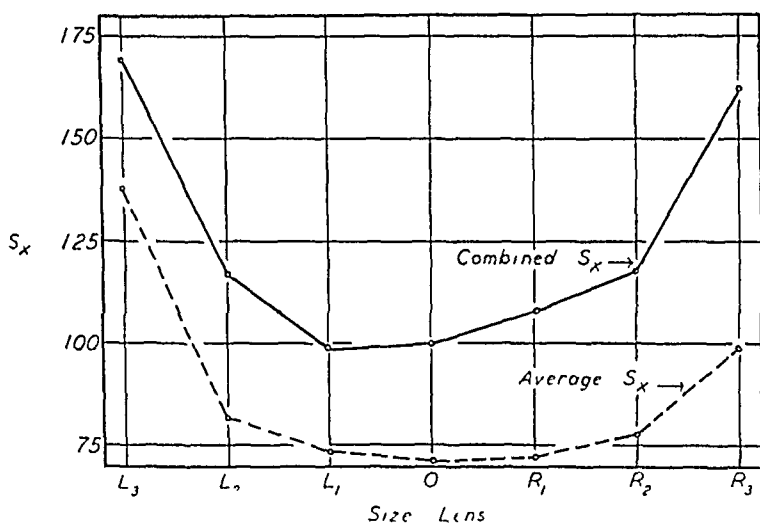


Fig 2—Effect of size lenses on the average and the combined threshold ( $S_x$ )

In the first paper of this series<sup>1</sup> it was stated that the difference between the  $E_s$  and the  $E_l$  was a measure of the degree of aniseikonia. In the present experiment, with the use of size lenses, aniseikonia was artificially created and the effect on the  $E_s$  was measured. It was found that size lenses alter the  $E_s$  in the expected manner, the lower power lenses altering it by the amount that would be expected, and the higher power lenses by an amount less than the calculated. The explanation of this trend toward instrumental zero could be based either on other cues of distance discrimination, which is unlikely, or on the time error, which is probable. The cause need not concern us here, since we are interested primarily in the effect of size lenses on the  $E_s$ , and this has been demonstrated to be of the type, if not of the magnitude, which would be expected. It is important that the  $E_s$  did vary in a systematic fashion with the use of the size lenses. Therefore,

the rod method of testing depth perception is clearly capable of measuring aniseikonia in the horizontal meridian, provided that the  $E_s$  can be calculated. In a former paper<sup>2</sup> it was shown that certain of the tests for distance discrimination, such as the "telebinocular" and the "stereopter" test, do not yield a position of subjective equality. This is an important consideration in the choice of tests, since the measure ( $E_s$ ) seems to be a valuable aid in detecting aniseikonia and, with standardization of technic and elimination of the time error, could probably be made to yield a reasonably accurate measure of the degree of aniseikonia.

While a rod type of test would probably not take the place of the eikonometer as a means of determining the degree of aniseikonia, if administered in such a manner as to yield a position of subjective equality ( $E_s$ ), it would serve as a valuable screening device. It possesses the simplicity and inexpensiveness which are desirable in such tests. The time necessary for the measurement and calculation is relatively short as compared with the many hours necessary to make an eikonometric determination. It should be stressed here that the Howard-Dolman test as used today does not yield this information, since the average deviation from the position of instrumental equality ( $E_i$ ) is used, rather than the position of subjective equality ( $E_s$ ) and the threshold ( $S_x$ ). By increasing the number of observations and by calculating the two measures just mentioned, this test could be made to yield much information about visual function which is at present not made available.

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# RESULTS OF SURGICAL TREATMENT OF CONGENITAL CATARACT

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THERE are few statistical studies on the results of operation for congenital cataract or on the various factors which influence these results<sup>1</sup> Hence, the best method of treating patients with this defect and the visual result to be expected have not been definitely established<sup>2</sup> To obtain more information on this subject, a study was made of 148 patients with congenital cataract The study included an analysis of the results of operations performed on 231 eyes at the Wilmer Ophthalmological Institute between January 1925 and October 1943 The fol-

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From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital

Read before the Section on Ophthalmology at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N J, June 12, 1947

1 Horay, G Ueber Staroperationen im Kindestalter, *Klin Monatsbl f Augenh* **74** 178, 1925 Klare, D Klinische Erfahrungen bei der operativen Behandlung des grauen Staes im Kindesalter, *Arch f Augenh* **102** 165, 1930 Kiss, W Sehstarfe der in fruher Kindheit doppelseitig Staroperierten, *Klin Monatsbl f Augenh* **98** 523, 1937 Falls, H F Developmental Cataracts, *Arch Ophth* **29** 210 (Feb) 1943

2 Ziegler, S H Complete V-Shaped Discission for Zonular and Pyramidal Cataracts, *J A M A* **77** 1100 (Oct 1) 1921, *Am J Ophth* **5** 381, 1922 Bell, G H Operation for Juvenile Cataract in Two Stages, *ibid* **9** 433, 1926 Dean, F W Cataracts Operation for Congenital and Juvenile, *Tr Am Acad Ophth* **31** 261, 1926 Alexander, G F The Immediate Removal of Congenital Cataracts, *Tr Ophth Soc U Kingdom* **48** 94, 1928 Barkan, O A Procedure for Extraction of Congenital, Soft, and Membranous Cataracts, *Am J Ophth* **15** 117, 1932 Green, J, and Beisbarth, C Congenital Cataract Extraction by Method of Barkan, *ibid* **16** 603, 1933 Ballantyne, A J Posterior Needling in the Treatment of Lamellar and Other Forms of Soft Cataract, *Brit J Ophth* **20** 540, 1936 von Hofe, K Beitrag zur Frage der Berufsfahigkeit derjenigen die in der Jugend wegen angeborenen Stars operiert wurden, *Arch f Augenh* **110** 34, 1937 Flesicher Zeitpunkt fur die operation eines angeboren Staes, *Klin Monatsbl f Augenh* **103** 329, 1939 Wolfe, O Removal of Soft Cataract by Suction, *Arch Ophth* **26** 127 (July) 1941 Boley, J P Some Practical Points on Congenital Cataract, *Bull Acad Med Toronto* **18** 197, 1945 Moncreiff, W F Contributions to the Surgery of Congenital Cataract, *Am J Ophth* **29** 1513, 1946



low-up period for the group ranged from no return visit to a maximum of twenty-two years, the average period being nineteen months.

The importance of various factors on the final visual result was first studied. These factors were then analyzed for their influence on the occurrence of operative or postoperative complications and on the necessity of secondary operations.

#### FACTORS INFLUENCING FINAL VISUAL RESULT

*Associated Ocular Defects*—The first factor found to be of significance was the presence of associated ocular defects. In this series, 129 eyes (55.8 per cent) had associated ocular defects, and 102 eyes (44.2 per cent) had no associated defects. Nystagmus, monocular strabismus and microphthalmos were the commonest defects (table 1). Monocular strabismus was considered an associated defect only when the operation had been performed on the deviating eye. As a rule, operations

TABLE 1—*Ocular Defects Associated with 129 Eyes with Congenital Cataract*

Nystagmus alone	53
Monocular strabismus *	27
Microphthalmos	12
Nystagmus and monocular strabismus *	15
Nystagmus and microphthalmos	13
Monocular strabismus and microphthalmos	3
Nystagmus and monocular strabismus* and microphthalmos	5
Pigmentary degeneration of retina	1
Total	129

\* Operation was always on the squinting eye.

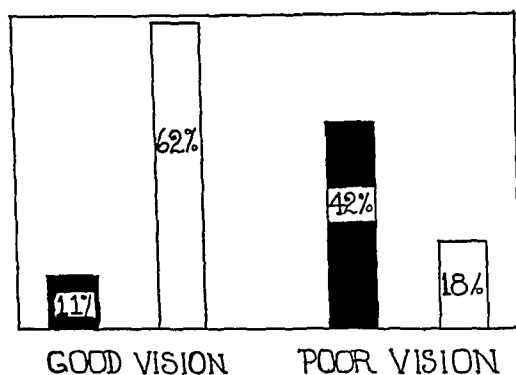
on eyes with strabismus were done on patients with bilateral cataract only after the cataract had been removed from the fixating eye.

The final visual acuity was known in 99 eyes with associated ocular defects and in 93 eyes without associated ocular defects. Good vision, that is, 20/70 or better, was obtained in only 11 per cent of the eyes with associated ocular defects but was obtained in 62.4 per cent of the eyes without such defects (chart). On the other hand, poor vision, a final vision of less than 20/200, resulted in 42.5 per cent of the eyes with ocular defects, but in only 18.3 per cent of the eyes without such defects. Thus, the presence of associated ocular defects was the first, and indeed, the most important, cause of poor vision.

*Age at Operation*—There has been a difference of opinion as to the proper time for the surgical treatment of congenital cataract. Early removal of the cataract has been advocated to prevent amblyopia ex anopsia.<sup>3</sup> On the other hand, postponement of the operation has been recommended because of the greater frequency of postoperative com-

3 Broendstrup, P. Amblyopia ex Anopsia in Infantile Cataract, *Acta ophth* 22:52, 1944. Goar, E., and Potts, C. The Relationship of Rubella in the Mother to Congenital Cataracts in the Child, *Am J Ophth* 29:566, 1946.

plications thought to accompany early intervention<sup>4</sup> At first glance, it would appear that this question might be readily answered by a comparison of the results obtained by early operation, i.e., before  $2\frac{1}{2}$  years of age, with those obtained by later operation The answer, however, is not so simple In evaluating the results obtained with operation at various ages, one must consider the presence of associated ocular defects at these ages In this series, the eyes operated on at an early age had a higher percentage of ocular defects than those operated on at a later age Thus, associated ocular defects were present in 72.5 per cent of the eyes in which operation was performed when the patient was  $2\frac{1}{2}$  years of age or under, while such defects were present in only 48.6 per cent of the eyes in which operation was deferred until the patient was over  $2\frac{1}{2}$  years of age When the visual results in eyes



Relation of final (postoperative) visual acuity to associated ocular defects in eyes with congenital cataract. Black rectangles show results for eyes with associated ocular defects, plain rectangles, values for eyes without such defects

having associated ocular defects are separated from those in eyes without defects, the factor of age can be independently evaluated

The results of such an analysis are shown in table 2 First, of the eyes without associated ocular defects, good vision (20/70 or better) followed operation in only 9.1 per cent when the patient was less than  $2\frac{1}{2}$  years of age, whereas good vision was obtained in 69.5 per cent of the eyes when operation was performed after the age of  $2\frac{1}{2}$  years Poor vision (less than 20/200) resulted in 36.3 per cent of the eyes when operation was performed before the age of  $2\frac{1}{2}$  years and in only 15.9 per cent when it was done after the age of  $2\frac{1}{2}$  years

<sup>4</sup> Wilder, W. H. The Operative Procedures and Methods of Handling Juvenile Cataracts, *Tr. Am. Acad. Ophth.*, **33** 113, 1928. Knapp, A. Operative Prognosis of Congenital Cataract, *Arch. Ophth.* **32** 519 (June) 1944. Moore, F. Diathermy in Ophthalmology, *Tr. Ophth. Soc. U. Kingdom* **53** 487, 1933. Shapland, C. D. Retinal Detachment in Aphakia, *ibid.* **54** 176, 1934. Philips, S. Treatment and Post-Operative Care of Cataract in Children, *M. Press* **216** 376, 1946.

Second, of the eyes with associated ocular defects, good vision resulted in 14.3 per cent of the eyes of patients over  $2\frac{1}{2}$  years of age, but in none of the eyes of patients under  $2\frac{1}{2}$  years of age. On the other hand, poor vision was obtained in only 3.5 per cent of the eyes of patients over  $2\frac{1}{2}$  years of age and in 68.2 per cent of the eyes of patients less than  $2\frac{1}{2}$  years of age at the time of operation. These results indicate that both in patients with and in patients without associated ocular defects, the final visual result is better when operation can be postponed until the patient is at least  $2\frac{1}{2}$  years of age.

*Type of Cataract*—The maturity of the cataract at the time of operation has been considered an important factor in determining the final visual result. In 52 eyes the cataracts were complete, being entirely

TABLE 2—*Relation of Age at Operation for Congenital Cataract to Final Vision*

Associated Ocular Defects	Age at Operation, Years	Number with Known Vision	Final Vision		
			20/70+, per Cent	20/100 to 20/200, per Cent	Less than 20/200, per Cent
None	Less than $2\frac{1}{2}$	11	9.1	54.5	36.3
	More than $2\frac{1}{2}$	82	60.5	14.6	15.9
Present	Less than $2\frac{1}{2}$	22	0.0	31.8	68.2
	More than $2\frac{1}{2}$	77	14.3	50.7	35.0

TABLE 3—*Relation of Type of Cataract to Final Vision*

Type of Cataract	Number with Known Vision	Final Vision		
		20/70+, per Cent	20/100 to 20/200, per Cent	Less than 20/200, per Cent
Complete	45	37.8	22.2	40.0
Incomplete	147	35.4	36.7	27.9

mature in 50 and membranous in 2. In 179 eyes the cataract was incomplete. In all of the latter, portions of the lens were clear. The group of incomplete cataracts included zonular, nuclear, punctate, fusiform, coralliform and anterior and posterior polar cataracts. The series of complete cataracts and the series of incomplete cataracts were entirely comparable in regard to the age of the patient at operation and the presence of associated ocular defects. A direct comparison of the visual results can, therefore, be made. The results of such a comparison are shown in table 3. It was found that the maturity of the cataract had no significant relation to the final visual acuity, the final visual results in the two groups being statistically similar.

*Method of Extraction*—In 70 eyes the cataract was removed by one or by repeated simple discissions. The discission was generally made only through the anterior capsule of the lens, but in a few cases

the posterior capsule was also incised. In all cases the lens was stirred after opening the capsule. In 62 eyes the cataract was removed by linear extraction. In these eyes, the anterior chamber was entered with a keratome, a large portion of the anterior capsule of the lens was removed with toothed forceps, and the lens substance was lavaged and expressed from the eye. In 73 eyes the cataract was removed by a combination of discission and subsequent linear extraction. In this group the preliminary discission was followed by a linear extraction after the lens substance had become flocculent, usually three days to two weeks later.

There was no significant relation between the method of operation and the final visual result in the eyes with associated ocular defects.

TABLE 4—*Relation of Operative Method to Final Vision in Eyes with Associated Ocular Defects and in Patients Operated On When Less Than 2½ Years of Age*

Associated Ocular Defects	Method	Number with Known Vision	Final Vision		
			20/70, per Cent	20/100 to 20/200, per Cent	Less than 20/200, per Cent
Eyes With Defects					
Patients less than 2½ years	Discission	11	0 0	27 2	72 8
	Linear extraction	9	0 0	22 2	77 8
	Discission followed by subse- quent linear extraction	2	0 0	100 0	0 0
Patients over 2½ years	Discission	20	10 0	50 0	40 0
	Linear extraction	19	10 5	42 0	47 5
	Discission followed by subse- quent linear extraction	22	18 2	54 5	27 3
Eyes Without Defects					
Patients less than 2½ years	Discission	4	25 0	25 0	50 0
	Linear extraction	3	0 0	66 0	33 0
	Discission followed by subse quent linear extraction	4	0 0	75 0	25 0

or in the eyes in which operation had been performed while the patient was less than 2½ years of age. The statistically similar visual results in these two groups are shown in table 4.

However, in the eyes without associated ocular defects, when the operation was performed after the patient was 2½ years of age, there was a significant relation between the method of operation and the final vision. These results are shown in table 5. Linear extraction or a combination of discission and subsequent linear extraction was superior, giving good visual results in 76.3 and 78.4 per cent of the eyes, respectively, whereas simple discission or repeated discission alone gave good visual results in only 28.6 per cent.

Intracapsular extraction was attempted in 14 eyes and was successfully accomplished in 8. Of the patients for whom the operation was successful, 1 was 3 years old, 3 were between 20 and 30 years of age,

and 4 were over 30 years of age. Three patients were without associated ocular defects, and all these obtained a final vision of 20/30 or better. Of the 5 patients with successful intracapsular extractions who had associated ocular defects, 2 obtained 20/70 vision, 2, 20/200 vision, and 1, vision of less than 20/200. Of the 6 patients in whom the capsule ruptured, 1 was between 20 and 30 years of age, and 5 were over 30 years of age. Of the 3 of these patients without associated ocular defects, 2 obtained final vision of 20/20 or better, and 1 had a final visual acuity of 20/200. Of the 3 patients with associated ocular defects, 2 obtained 20/100 vision, and 1, 20/200 vision. It appears, therefore, that in this small series rupture of the capsule at operation had no appreciable effect on the final vision.

Extracapsular extraction was performed on 11 eyes. Four eyes had no associated ocular defects, and good vision was obtained in 2 of them.

TABLE 5—*Relation of Method of Operation to Final Vision in Eyes with No Associated Ocular Defects Operated On When Patient Was Over 2½ Years of Age*

Method of Operation	Number with Known Vision	Final Vision		
		20/70+, per Cent	20/100 to 20/200, per Cent	Less than 20/200, per Cent
Discission	14	28.6	35.7	35.7
Linear extraction	21	76.3	9.5	14.3
Discission followed by subsequent linear extraction	37	78.4	13.5	8.1

#### COMPLICATIONS

The first section of table 6 shows the incidence of various complications in eyes with associated ocular defects and in eyes without such defects. There was no statistical difference in the incidence of complications in these two groups. Similarly, there was no significant relation between the occurrence of complications and the age of the patient at the time of operation (table 6, second section). Likewise, there was no difference in the incidence of complications in patients with mature and in patients with immature cataract (table 6, third section).

Table 7 shows the relation of operative and postoperative complications to the method of operation. The higher incidence of loss of vitreous with linear extraction and with discission and subsequent linear extraction is, of course, a reflection of the wider opening of the anterior chamber and the manipulations required in these operations. Other complications occurred with almost equal frequency with the three methods of cataract extraction: simple discission, linear extraction and discission with subsequent linear extraction.

Of the 14 cases of attempted intracapsular extraction, loss of vitreous occurred in 4, secondary glaucoma developed in 2 and post-operative iridocyclitis occurred in 1. Thus, in this small series, there was no increase in the incidence of iridocyclitis, but loss of vitreous and secondary glaucoma were definitely more frequent than with the other methods of extraction.

Gaping of the wound and prolapse of the iris were infrequent complications. In only 2 cases in the entire series did gaping of the wound occur, and in only 1 did prolapse of the iris develop.

TABLE 6—*Incidence of Complications*

	Number of Cases	Loss of Vitreous, per Cent	Hemorrhage in Anterior Chamber, per Cent	Irido cyclitis, per Cent	Endoph thalmitis, per Cent	Secondary Glau coma, per Cent	Detach- ment of Retina, per Cent	Phthisis Bulbi, per Cent
Associated Ocular Defects								
None	102	16.7	5.9	3.9	2.9	0.0	2.0	9.8
Present	129	10.1	3.1	6.2	0.0	5.4	1.6	3.9
Age at Operation (Years)								
Less than 2½	58	5.2	3.5	3.5	0.0	1.7	1.7	8.6
Over 2½	173	15.6	4.6	5.8	1.7	3.5	1.7	5.8
Type of Cataract								
Complete	52	9.6	3.9	11.5	0.0	1.9	1.9	7.7
Incomplete	179	14.0	4.5	3.4	1.7	3.4	1.7	6.1

TABLE 7—*Relation of Complications to Method of Operation*

	Number of Cases	Loss of Vitreous, per Cent	Hemorrhage in Anterior Chamber, per Cent	Irido cyclitis, per Cent	Endoph thalmitis, per Cent	Secondary Glau coma, per Cent	Detach- ment of Retina, per Cent	Phthisis Bulbi, per Cent
Dissection	70	1.4	0.0	4.3	1.4	1.4	0.0	7.1
Linear extrac- tion	62	16.1	6.5	8.1	1.6	3.2	3.2	8.1
Dissection followed by linear ex traction	73	17.8	6.9	0.0	1.4	2.7	2.7	5.5

Purulent endophthalmitis developed in 3 eyes in the series (1.3 per cent). In all cases it occurred before the sulfonamide drugs or anti-biotic substances were available and phthisis bulbi developed in all.

Nonpurulent iridocyclitis developed in 12 eyes (5.2 per cent) but subsided in all. Three of the eyes obtained good vision (20/70 or better). In 5 eyes numerous secondary operations were performed to clear the pupillary opening. In these eyes the iridocyclitis recurred, phthisis bulbi finally developing.

To determine the importance of sensitivity to retained lens material as a cause of postoperative nonpurulent iridocyclitis, intracutaneous

tests with lens protein were performed on 8 of the patients. In 3 there was strong cutaneous sensitivity to the protein, while in 5 the tests gave negative results. Nineteen control tests, on patients without postoperative iridocyclitis, were performed. None of these gave positive cutaneous reactions to the injected lens protein. In the 3 patients with nonpurulent iridocyclitis and pronounced cutaneous sensitivity to lens protein, the inflammation was thought to be endophthalmitis phacoanaphylactica. Two of these were desensitized to lens protein<sup>5</sup> before an operation was undertaken on the fellow eye. In each case, after the cutaneous sensitivity had been abolished the operation on the fellow eye was not followed with iridocyclitis.

Detachment of the retina occurred in 4 eyes (17 per cent). In 2 eyes operations for retinal detachment were performed. In one of these eyes the operation was successful, the patient obtaining 20/200 vision. In the other, the retina could not be reattached.

TABLE 8.—*Relation of Method of Operation to Subsequent Operations*

Method of Operation	Number of Cases	Subsequent Operations, per Cent			Total
		Discission	Capsulotomy	Capsulec- tomy	
Discission	70	40.0	15.7	10.0	65.7
Linear extraction	62	17.8	16.1	3.2	37.1
Discission followed by linear extraction	73	23.3	8.2	5.5	37.0

Secondary glaucoma occurred in 7 eyes (30 per cent). In 1 eye the glaucoma was transient, the tension being controlled without miotics. In 2 eyes the tension was controlled with miotics alone, while a third required cyclodialysis in addition. In the 3 remaining eyes the ocular tension could not be controlled even with miotics or operations.

#### SECONDARY OPERATIONS

No significant correlation was found between blocking of the pupil by capsular remains, with the consequent necessity of secondary operations to clear the pupillary space, and any of the following factors: presence or absence of associated ocular defects, age of the patient or maturity of the cataract at the time of the initial operation. However, when the initial operation was a simple discission, repeated discissions to clear the pupillary space were required in 40 per cent of the eyes. Table 8 shows that the frequency of secondary operations to clear the pupillary space was significantly higher (65.7 per cent) in the eyes operated on by discission alone than in the eyes operated on by linear extraction or by discission with subsequent linear traction (37.0 per cent).

<sup>5</sup> Hughes, W. F., Jr., and Owens, W. C. Postoperative Complications of Cataract Extraction, *Arch. Ophth.* **38**: 577 (Nov.) 1947.

## COMMENT

It is well known that the final visual result following removal of congenital cataract is much poorer than the result following the extraction of senile cataract. This has been attributed to the higher incidence of operative and postoperative complications thought to follow operations for congenital cataract. Such an increased liability to complications was not found in this series. Table 9 shows the incidence of operative and postoperative complications in the present series of cases of congenital cataract and in the series of cases of operations for senile cataracts previously reported.<sup>6</sup> In these two series, there was no significant difference in the incidence of complications in the operations performed for congenital cataracts and in those performed for senile cataract. Therefore, the poor visual results following the removal of congenital cataract cannot be attributed to more frequent complications.

What other factor can account for the poor vision following the removal of congenital cataract? Gross associated ocular defects were

TABLE 9—*Relative Incidence of Complications in Operations for Congenital and Senile Cataracts*

Type of Cataract	Number of Cases	Loss of Vitreous, per Cent	Hemorrhage in Anterior Chamber, per Cent	Iridocyclitis, per Cent	Endophthalmitis, per Cent	Secondary Glaucoma, per Cent	Detachment of the Retina, per Cent
Congenital	231	17.3	4.3	5.2	2.2	2.2	1.7
Senile	1,650	8.2	9.1	6.7	1.2	4.1	1.5

present in 55 per cent of the eyes with congenital cataract. In these eyes the final visual result was very poor, vision of 20/70 or better being obtained in only 11 per cent. However, even in the group with no gross associated ocular defects, the final visual results were poorer than those following the removal of senile cataract. In the present series the removal of congenital cataract from eyes with no gross associated ocular defects resulted in good vision (20/70 or better) in only 62.4 per cent. In the series previously reported the removal of senile cataract resulted in good vision in from 80 to 95 per cent of the eyes, according to the operative technique employed. Since the occurrence of complications following the removal of congenital cataract is essentially the same as that following the removal of senile cataract, it is possible that the eyes with congenital cataract and no gross associated ocular defects have obscure defects, such as incomplete or abnormal formation of the retinal elements. It is likely, therefore, that the overall poor visual results following removal of congenital cataracts must

<sup>6</sup> Hughes, W. F., Jr., and Owens, W. C. Extraction of Senile Cataract, *Am J Ophth* 28:40, 1945.



be attributed to the fact that many of the eyes with congenital cataract are otherwise defective and cannot be expected to have high visual acuity even when the cataracts are successfully removed

#### SUMMARY AND CONCLUSIONS

Gross associated ocular defects were present in 129 of 231 eyes with congenital cataract. The visual results in these eyes were significantly poorer than in the eyes without such gross ocular defects.

The visual results for the patients on whom the operation was performed before  $2\frac{1}{2}$  years of age were poorer than for those operated on after the age of  $2\frac{1}{2}$  years.

The visual results were essentially the same whether the congenital cataract was complete or incomplete at the time of operation.

Linear extraction or discission with subsequent linear extraction produced better visual results than simple discission in the patients with no associated ocular defects who were operated on after  $2\frac{1}{2}$  years of age.

Operative and postoperative complications were as frequent in the eyes without associated ocular defects as in the eyes with associated ocular defects. No significant relation was found between the occurrence of complications and the age of the patient or the maturity of the cataract at the time of operation.

The type of operation performed had no significant relation to the occurrence of postoperative complications.

The number of secondary operations necessary to clear the pupillary space was higher after simple discission than after linear extraction or discission with subsequent linear extraction.

Complications occur with essentially the same frequency after the extraction of senile as after extraction of congenital cataract. The poorer visual results after extraction of congenital cataract are attributed to either gross or obscure associated ocular defects.

Wilmer Ophthalmological Institute (Dr Owens)

University of Illinois School of Medicine (Dr Hughes)

#### ABSTRACT OF DISCUSSION

DR FREDERICK C CORDES, San Francisco. The authors found associated ocular defects in 55.8 per cent of the eyes with congenital cataract. This corresponds rather closely with the figures given by Fall, who found associated ocular defects in 52.6 per cent of a series of 131 patients. Thus, it is apparent that the prognosis must be guarded in the surgical treatment of congenital cataracts.

A visual acuity of 20/40 or better would seem to be sufficient to contraindicate operation, since the wearing of the heavy, disfiguring lenses is in itself a handicap to the growing child. In some instances,

as with the lamellar cataract, the opacity may increase in density so that operation may be necessary later

The statistics of Owens and Hughes would seem to indicate that operation should not be performed before the age of  $2\frac{1}{2}$  years because of the poorer results. Horay, in reporting the results in 282 operations for congenital cataract, stated that he considered unfounded the opinion that operation should be done after the first year. In his series the results were just as good for operations done in the first year of life as later. The failures during the first year were often the result of other congenital anomalies. Fuchs stated

The earlier the operation the better the visual result. Eyes with congenital cataract are usually smaller than normal and, if the lens is removed early, continue to be retarded in their growth. If one waits until later to operate, the eye will have increased some in size, but the visual acuity will be much worse because the retina, owing to lack of use, fails to develop normally.

From personal experience and from the literature, it would seem that in those cases of bilateral cataract in which the opacities are sufficiently dense to interfere with the development of fixation, the first eye should be operated on at the age of 6 months so that the child may develop this faculty, and thus perhaps avoid nystagmus.

Only approximately 50 per cent of these eyes have a postoperative vision of 20/70 or better. After the operation the child has to learn to see, as he lacks visual memories. Thus, vision must be developed through experience. In 1927 Fuchs said

One reads in romances how the congenitally blinded person is operated on, and how at the first removal of the dressings he is surprised at the beauty or homeliness of his adored ones. This must be regarded purely poetic fantasy.

The authors found that linear extraction or a combination of discission and subsequent linear extraction was superior to simple discission or repeated discissions. This is in agreement with Falls's experience, who in his series found that the best visual acuity was obtained when discission and linear extraction were used. Horay concluded that the operation of choice, irrespective of the age of the child, was a linear extraction done at one sitting. Thus, these three large series of cases indicate that repeated discission gives the poorest results.

My personal choice of operation in cases of soft congenital cataract is the linear extraction as modified by Otto Barkan. The important modifications are as follows: 1. Injection of epinephrine hydrochloride (1:1,000) at the limbus, at the site of the incision, to prevent the iris from becoming involved. It also keeps the pupil widely dilated during the operation. 2. Placing of the incision parallel to the surface of the iris and 1 to 2 mm. inside the cornea so as to obtain a valvelike incision. In addition, it has been found that the injection of air into the anterior chamber at the completion of the operation is an important factor in the prevention of anterior synechias and incarceration of the iris.

With certain types of congenital cataract, particularly the congenital membranous cataract, the discission as advocated by Wheeler is indicated.

In cases of the disk-shaped cataract, in which two types are present—a membranous central portion and a peripheral soft cataract—a discis-

sion followed later by an incision through the membrane with Berens or de Wecker scissors is usually necessary

In cases of cataract following rubella, in addition to the consideration of other possible anomalies, it is well to remember that the absorption of the lens substance is slower than that of the usual congenital cataract and that in most instances it is difficult to dilate the pupil with any mydriatic

DR WILLIAM C OWENS, Baltimore It was a great pleasure to have Dr Cordes discuss this subject, since he has been interested in it for many years I think that in essence he agrees with our results except for the question of the age at operation As he stated, this subject has been a controversial one for many years Further work will be necessary before the final answer will be available

## EFFECT OF A PRISM ON THE CORNEAL LIGHT REFLEX

EMANUEL KRIMSKY, M D

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ONE IS accustomed to think of a prism as a wedge-shaped piece of glass which bends a ray of light traversing it in the direction of its base. That this ray of light affects the position of the corneal light reflex in a paradoxical manner is not generally known.

Displacement of a corneal light reflex from a fixational position is known to indicate ocular deviation, and any artificial method which could restore such displacement to a fixational position can likewise serve to register the amount of such deviation. Such artificial restoration by binocular instruments employing flexibly moving lighted targets through a measured range is established practice. That a corrective prism could likewise restore a displaced corneal light reflex to a fixational position was noted by me in a previous report<sup>1</sup>.

Maddox,<sup>2</sup> in his excellent treatise entitled "The Clinical Use of Prisms," devoted a chapter to the internal reflection of images through a prism without suggesting its possible effect on the corneal light reflex. He rightfully stated<sup>2</sup> that "hitherto we have only considered the refraction of light by prisms, but at each surface a smaller portion is also reflected." He noted

the faint image of a flame viewed through the center of a prism points exactly to the apex of the prism, and it is curious that so simple a guide does not appear to have been hitherto utilized. Could we not utilize also the distance between the bright image of a flame and its faint image for measuring the strength of a prism?

Maddox made no mention whatever of the effect of a prism on the corneal light reflex. Although more than a half-century has passed since the publication of this memorable treatise, I take the liberty of repeating Maddox's words by stating that it is curious that so simple a guide as the artificial displacement of a light reflex on a cornea or a convex spherical mirror by a prism does not appear to have yet been utilized or reported in textbooks on optics or ophthalmology.

If one accepts the dictum that artificial restoration of the corneal light reflex from a displaced to a central or fixational position is a

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1 Krinsky, E. The Fixational Corneal Light Reflex as an Aid in Binocular Investigation, *Arch Ophth* 30 505-521 (Oct) 1943

2 Maddox, E. The Clinical Use of Prisms, London, John Wright & Sons, Ltd., 1893

prerequisite to the measurement of squint, one must likewise think of a prism as a medium which should also produce such a corrective effect. In a previous report, I emphasized that such displacement must be toward the apex of the prism, and not the base. If, for example, one thinks of esotropia as registering temporal displacement of the corneal light because the eye is turned in, one might make the mistake of assuming that a base-out prism, which bends a ray of light toward its base, would displace the light reflex still more temporally in the direction of the base. If such a phenomenon were possible, one would be at a loss to explain binocular fixation in terms of centralized corneal light reflexes. If such an apparently strange phenomenon of apical displacement of a corneal light reflex does occur with prism, it is because with such a light reflex one thinks in terms not of refraction but of reflection of light or image displacement, analogous to looking through a prism and seeing an image displaced apically.

To simplify matters, one may regard the cornea as a convex spherical mirror or a reflecting medium. As a curved mirror, it is composed of a multitude of plane mirrors or tangents to this curved surface. To make matters still simpler, one may begin with a plane mirror and see how its reflecting properties are modified when it is rotated (deviated) and then when a prism is interposed.

#### LAWS OF REFLECTION IN RELATION TO A PLANE MIRROR<sup>3</sup>

Not only will a light the rays of which cross or strike a plane mirror yield a virtual, erect image, but this image will appear to be as much behind the mirror as the object light is in front of it. Moreover, this object light will produce an image of exactly the same size.

If the examiner's testing eye (or camera lens) and the light source are in direct line and perpendicular to the axis of mirror (fig 1), the image will likewise appear in a continuous line with the observer's eye. Though the light that emanates from a flashlight consists of pencils or rays of light which spread out in different directions, it is only the particular wave or waves in direct line with the mirror which govern the image response as seen in the mirror. If a flashlight is tilted at a considerable angle and directed almost parallel to, instead of perpendicular to, the surface of the mirror, it is still those selective rays perpendicular to the surface of the mirror which govern the so-called light reflex in the corneal mirror.

As the light is moved back and forth from the mirror in a direct perpendicular axis, one sees a corresponding fore-and-aft displacement of the light reflex in the mirror. With a corneal convex mirror axial displacement would hardly be apparent because of the very small radius of curvature of the mirror.

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3 Cowan, A. Ophthalmic Optics, Philadelphia, F. A. Davis Company, 1927

If the flashlight is kept in direct perpendicular axis to the mirror, but the observer's eye or camera lens is shifted to one side, the light reflex will no longer appear to be coming straight toward him, but will appear to be coming from a side. This parallax displacement of the image in a plane mirror is greater than that in a spherical mirror, even though the axial relationship of the object light and the image light is not disturbed. The eye of the observer, by shifting its position away from this fixed perpendicular axis, sees the reflex image likewise as displaced.

Displacement of the reflex image in a mirror can also be produced by rotating the mirror on its vertical axis or edge through a central rotating point without upsetting the fixed relation of the camera lens or the testing eye behind the flashlight. Whether one rotates the mirror

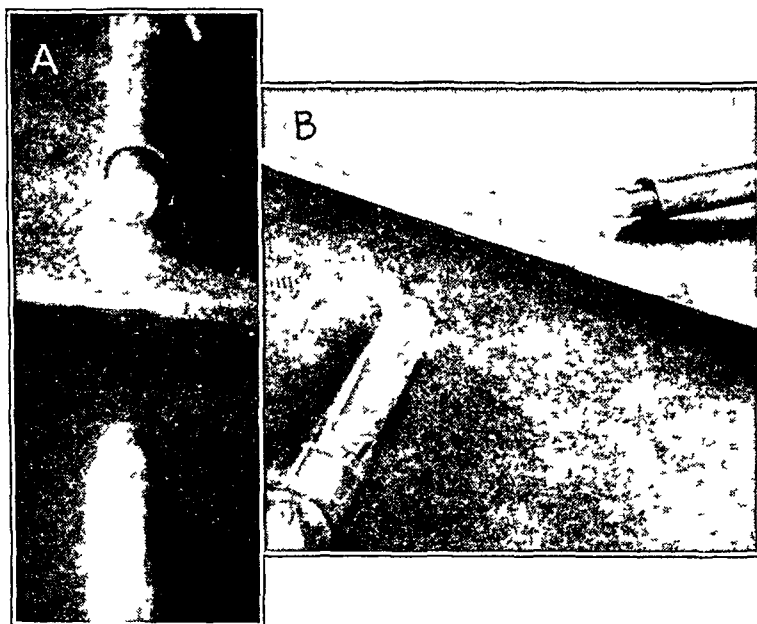


Fig 1—Reflection by a plane mirror (A) The light seen through a mirror placed at right angles to the source of light will be seen to register a light reflection, or "reflex," directly opposite, or facing, the object light. The same effect is observed when the examiner sees the light reflex in a fixing eye with his eye directly behind the test light.

(B) Without change in the positions of the observer's eye and the test light, the mirror is now tilted on its edge or "rotated." The light reflection is now seen to move to one side, in the same way as though the eye were rotated from its position of fixation. In this case, the light reflex is displaced to the right of the object light in the same way as though the left eye facing the examiner were to rotate to the right.

As a plane or a convex mirror is rotated, one observes the position of the light reflection to change accordingly. The examiner translates this displacement in terms of the new direct path between his eye and the reflection at the principal focus, where it intersects the corneal mirror.

(or merely rotates an eyeball) or/and changes the position of the eye behind the test light, the position of the reflex image is based on the simple law of the angle of incidence and the angle of reflection (figs 1 and 2)

## DISPLACEMENT OF IMAGE BY PRISM VERSUS MIRROR

The effect of rotating a plane mirror on its edge, or vertical axis, in producing displacement of an image is not unlike what one would find in looking through a prism. One can note, furthermore, that such rotation of a mirror through a measured amount will produce displacement of an image equal to that produced by a prism of a strength equivalent to the angle of rotation. For example, if it is assumed that 20 arc degrees equals roughly 37  $\Delta$ , then a mirror rotated around a central vertical axis over a protractor reading of 20 degrees will produce an equivalent image displacement. Rotation of the mirror which

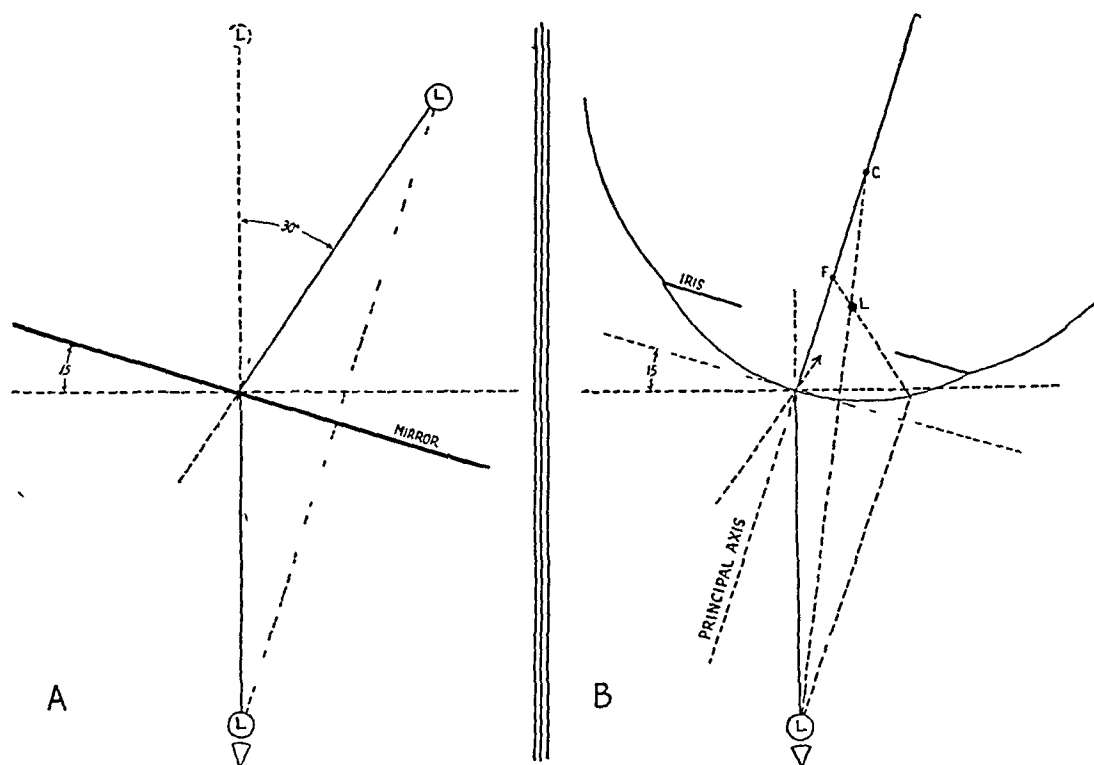


Fig 2—Effect of mirror “rotation” on the position of the light reflection A, with plane mirror, B, with convex mirror (cornea)

brings the right half nearer the camera will also produce reflex displacement to the right (figs 1 and 2). The apex of the prism placed to the right with the flashlight at right angles to the mirror will produce the same effect. A combination of prism and mirror in such positions would produce a summation of effect. However, placement of prism and mirror in reverse positions will have a neutralizing effect, and not only will the reflex image be directed toward the apex but the direction of the flashlight axis as seen through the prism will appear rectified in a straight continuous line with that of the object light, in other words, the angulation of the lines as a result of mirror rotation will be trans-

formed into a continuous straight line, and the flashlight image will appear to be coming directly toward the observer's eye and will no longer be angulated. This phenomenon (fig 3) is interesting, for it serves to indicate that the effect of a prism is not merely to restore a reflex image to a central, or fixational, position but also to restore the image of the axis to a continuous straight line. This phenomenon, moreover, is of interest because in actual ocular deviation one learns to think of a prism as a medium not only for restoring the light reflex to a central, or fixational, corneal position but also for rectifying the image along this bent visual axis and making the eyeball actually appear straight.

#### REFLECTION FROM A CONVEX MIRROR

If one can conceive of a spherical mirror or the eye as a collection of plane mirrors arranged tangentially around different points of the circle, it becomes easier to understand the disposition of the lighted image or of reflections behind its surface. A luminous spot directed toward a convex mirror will, provided the eye of the observer is behind the test light, be seen to proceed through the mirror without interruption to focus at a point halfway between the surface of the sphere and the center of rotation. This point is known as the principal focus. Why does the light reflex take its position at this point? It is because the divergent rays reflected from any tangent on the convex sphere will be reflected back not to the center of the sphere but to the aforementioned midway point, which is called the principal focus. Unlike the image in the plane mirror, the image as seen through a convex spherical mirror is also virtual and erect but is nearer the surface than the object light. The smaller the radius of curvature, the closer to the surface this light reflex becomes, although as long as the surface is a sphere the light reflex is at or near the principal focus, or halfway between the center of curvature and its surface.

As in the case of the plane mirror one would like to know how the light reflex image is displaced when the testing eye alone is moved away from the principal axis along which the light stimulus is directed. Then one might wish to know the variations in position of the light reflex when the testing eye alone is in line with the principal axis and only the test light is moved into different positions. In the latter instance, with the testing eye in line with the principal axis, the respective positions of the light reflex as a result of such changing positions of the test light are shown in figure 7. Only when the light is in a direct line with that of observer and patient will it after reflection return along the same path. Light moved to any other point will be seen to move in a corresponding direction, although through a smaller linear range than in the case of the plane mirror.



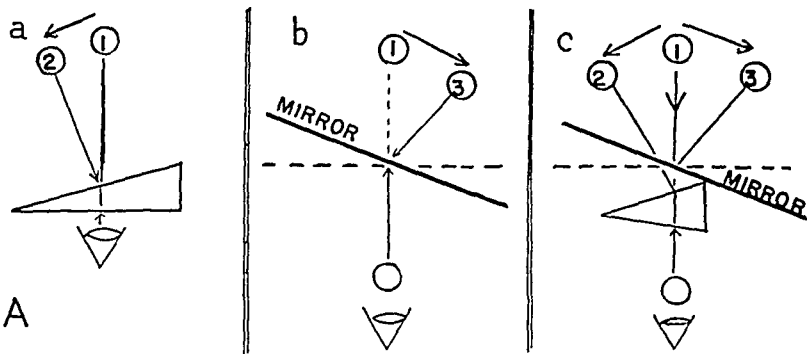


Fig 3—Displacement of image or light reflection by prism as compared with displacement by mirror *A*, schematic drawings, *B*, photographic demonstration

(*A*) In *a*, the image as seen through the prism shifts from position 1 obliquely forward and to the left, or toward the apex of the prism to position 2. In *b*, a mirror is substituted for a prism and is so "rotated" on its edge (as in fig 1 *B*) as to shift the light reflection obliquely forward in the opposite direction. In *c*, the effect of both mirror and prism placed in the aforementioned positions serves to restore the light "reflex" to a central position by prism and mirror counteracting the effects of each other.

(*B*) This photograph portrays vividly the mechanism of the prism reflex test. The object test light is in the lower left corner. The plane mirror is tilted at an angle, as in figure 1 *B*, with the right half nearer the camera. Therefore, when one ignores the prism, the light reflection by mirror alone is the farthest to the right. That reflection is comparable to the reflex in the left eye as seen by the observer to be rotated to his right, thereby causing apparent displacement of the light reflex temporally. The plane mirror is comparable to the cornea.

A square prism is placed in front of this mirror, and an image of this prism is also observed in the mirror. One also notes three light "reflexes," the aforementioned one, without the prism, a second, seen through the image prism alone, and a third, seen through the object prism. Observe that the light reflex is displaced toward the apex of the prism, rather than toward the base. Note also that the third "reflex," through the object prism, appears to be coming face to face with the object light. This phenomenon is especially interesting and significant, for it shows that the action of a prism is not merely to shift the image in the direction of the apex of the prism, but also to rectify the course of this image, or to neutralize the tilting of the mirror. The three reflexes are interdependent. Which of the three reflexes determines the deviating property of the prism? The answer is the third, or object "reflex." The second, or middle, "reflex" displaces the image only halfway through the image prism. The third, or object prism, "reflex" represents the added displacement of the image prism through the object prism. Note the edge of the image prism through the object prism. In clinical testing with prisms one always looks through the object prism instinctively to observe the light reflex.

## POSITION OF THE CORNEAL LIGHT REFLEX

If one is to think of the cornea as a convex spherical mirror, light rays which strike it should meet at or near a common point. This point is the principal focus of the cornea and is situated about 4 mm behind its

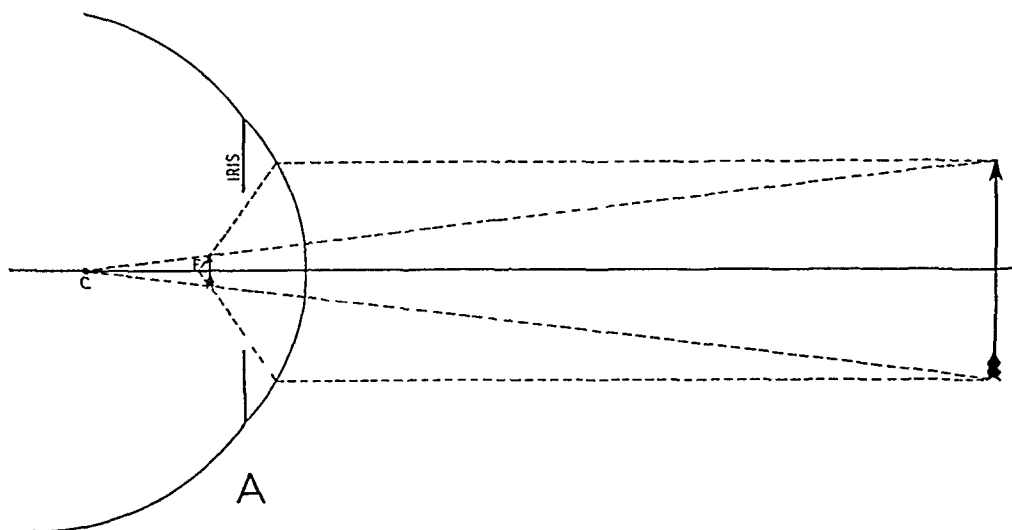


Fig 4—Relative sizes and positions of images or light reflections with convex and plane mirrors, respectively

*A*, diagram illustrating that the corneal light reflex is in reality a subcorneal light reflection of reduced size, and showing that a prism placed in front of an eye registers a reduced size of image prism behind the cornea

*B*, photograph showing comparative sizes of light reflections in plane and convex mirrors, respectively. In the plane mirror, the image size is the same as the object size, in the convex mirror over it, the image of the flashlight is smaller, and, finally, in the corneal convex mirror, of very short radius, the light reflex is rather small

anterior surface, it being assumed that the cornea has a radius of curvature of 8 mm. Hence, the term corneal light reflex is a misnomer because the light reflex is subcorneal (fig 4) in position and technically is a reflection rather than a reflex.

A light that strikes the eyeball at an angle is seen to produce several images, known as the images of Purkinje because of structural components, such as the lens, seen in the path of the light rays.<sup>4</sup> The familiar corneal light reflex is therefore technically but one of these five or six Purkinje images and is said to be deposited in the region of the anterior surface of the lens. It is the brightest of these images and is erect and virtual. Because it also exists in an aphakic eye, I prefer to discount the corneal light reflex in terms of Purkinje images and to think of it solely in terms of a principal focus image, like that which one might find with any spherical ball. Its relation to the anterior surface of the lens is merely incidental, because that is where one finds the principal focus of the cornea.

The intersection of the different points from parallel rays will determine both the position and the size of the image. The importance of appreciating the position of the light reflex in relation to the position of the observer's eye may be illustrated by the following mathematical example.

An eye fixing a point source of light at a distance of 33 cm is found to register a corneal light reflex on the center of the pupil as long as the observer's eye is behind the test light. Where would the light reflex appear to be on the cornea if the observer's eye were moved 60 degrees along the arc of the angiometer while the examinee's eye maintains fixation on the light source? In figure 5 the light reflection is behind the cornea at a point on the principal axis halfway between the cornea and the center of curvature. When an eye is moved 60 degrees along the arc, the corneal light reflection will appear to move from point *S* to point *O* on the cornea. The following formulas with the aid of the diagram (fig 5) are self explanatory.

$$\text{Angle OFS} = 60^\circ$$

$$SF = 4 \text{ mm}$$

$$FC = 4 \text{ mm}$$

$$OC = 8 \text{ mm}$$

$$\sin B = \frac{b \sin A}{a}$$

$$\sin B = \frac{4 \text{ (mm)} \times 0.866 (\sin A)}{8 \text{ (mm)}}$$

$$\sin B = 0.433 = 25^\circ 42'$$

Angle OFC =  $120^\circ$       Angle C =  $180^\circ - (120^\circ + 25^\circ 42') = 34^\circ 18'$   
 which is equivalent to 4.7 mm off center of the cornea, based on a corneal circumference of about 50 mm

<sup>4</sup> Wood, C. A. The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1916, vol 8, p 6174

This case illustrates the importance of the examiner's keeping his own eye directly behind the test light in order to avoid error in interpreting the position of the fixational corneal light reflex. In this instance the examiner who keeps his own eye 60 degrees away from the test light is introducing an error of  $34^{\circ}18'$  in relation to the true fixational position of the corneal light reflex.

#### SIZE OF CORNEAL IMAGE IN RELATION TO SIZE OF TEST OBJECT

The size of the corneal light reflex has a direct bearing on the size of the test light. This is of definite practical importance, for when the test light is large the corneal light reflex likewise is large and

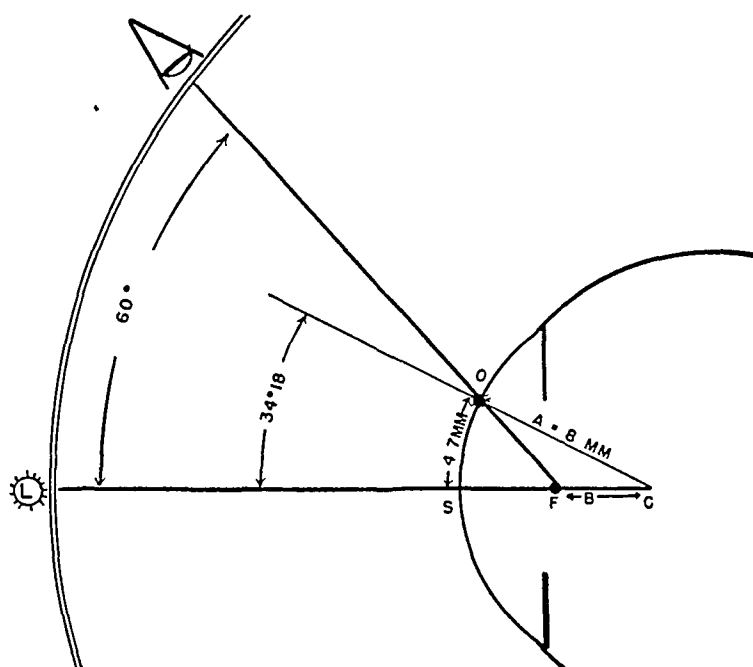


Fig 5—Diagram showing how relative positions of the examiner's eye and the test light affect the position of the corneal light reflex.

The diagram is explained in the text.

therefore consumes more of the pupillary area. A corneal light reflex of the smallest possible size to permit critical inspection should therefore prove most satisfactory. Moreover, the light source should be bright, but not so intense as to produce a glaring effect. A medium-sized flashlight with good reflector should prove satisfactory.

Not only is a test light imaged behind the cornea, but one can also observe one's face, reduced in size, and, in the case of a prism over the eye, a reduced image of the prism if one looks between the object prism and the image prism.

The following example will serve to illustrate the relative sizes of object prism and image prism, depending on the distance, as well as the size of said object from the cornea (fig 4).

A A prism is placed 10 mm from the cornea Where behind the cornea does the image of the prism appear to be?

Formula

$$f = \text{distance from prism to cornea} \quad \frac{1}{f} + \left(-\frac{1}{f'}\right) = -\frac{1}{F}$$

$$f' = \text{distance from cornea to image} \quad \frac{1}{10} + \left(-\frac{1}{f'}\right) = -\frac{1}{4}$$

$$F = \frac{1}{2} \text{ radius of curvature of cornea} \quad \frac{1}{f'} = 2.86 \text{ mm behind anterior surface of cornea}$$

(8 mm) = 4 mm

B What is size of the image of a prism 40 mm square placed 10 mm from the cornea?

Formula

$$O = \text{length of prism, or 40 mm} \quad \frac{I}{O} = \frac{f}{f'}$$

$$f = \text{prism to cornea, or 10 mm} \quad \frac{I}{40} = \frac{2.86}{10}$$

$$f' = \text{cornea to image, or 2.86 mm (as determined in preceding formula)} \quad I = 40 \times \frac{2.86}{10} = 11.44 \text{ mm}$$

#### DEVIATION OF A CORNEAL LIGHT REFLEX PRODUCED BY A PRISM

It was shown previously that a prism acts much like a mirror. When a mirror is rotated on its vertical axis, the image seen through it can be rectified to an apparently neutral position by interposition of a prism producing an opposite, or neutralizing, effect. What is true of a plane mirror is true also of a curved mirror. Figure 6 shows the parallel relation of the two systems of mirrors. It follows, therefore, that if a prism can rectify the axial displacement of the image in a plane mirror, as well as "correct" the position of the light reflection, it should do the same with a curved mirror. It is this simple displacement which explains the prism reflex test.

Suppose one looks at the image of a point source of light formed either by a plane mirror or by a convex spherical mirror, keeping the eye near the light source. If a prism is interposed in such a way that the image is seen through the prism, the image appears to move toward the vertex of the prism. In the discussion which follows, I shall consider the case in which both the light from the source, and incident on the mirror, and the light reflected from the mirror, and going to the eye, pass through the prism.

One is concerned here with virtual images. A virtual image is defined as one from which the rays of light appear to come. In the figures, the actual paths of the light rays are shown by the solid black lines, and the formation of the virtual images is shown by the interrupted lines. It should be pointed out that a prism will form virtual images only if the vertex angle of the prism and the angular spread

of the cone of rays are both rather small. The diagrams are idealized in that the angular spread of the cone of rays shown is larger than would be permissible. Because of the small angular spread of the cone

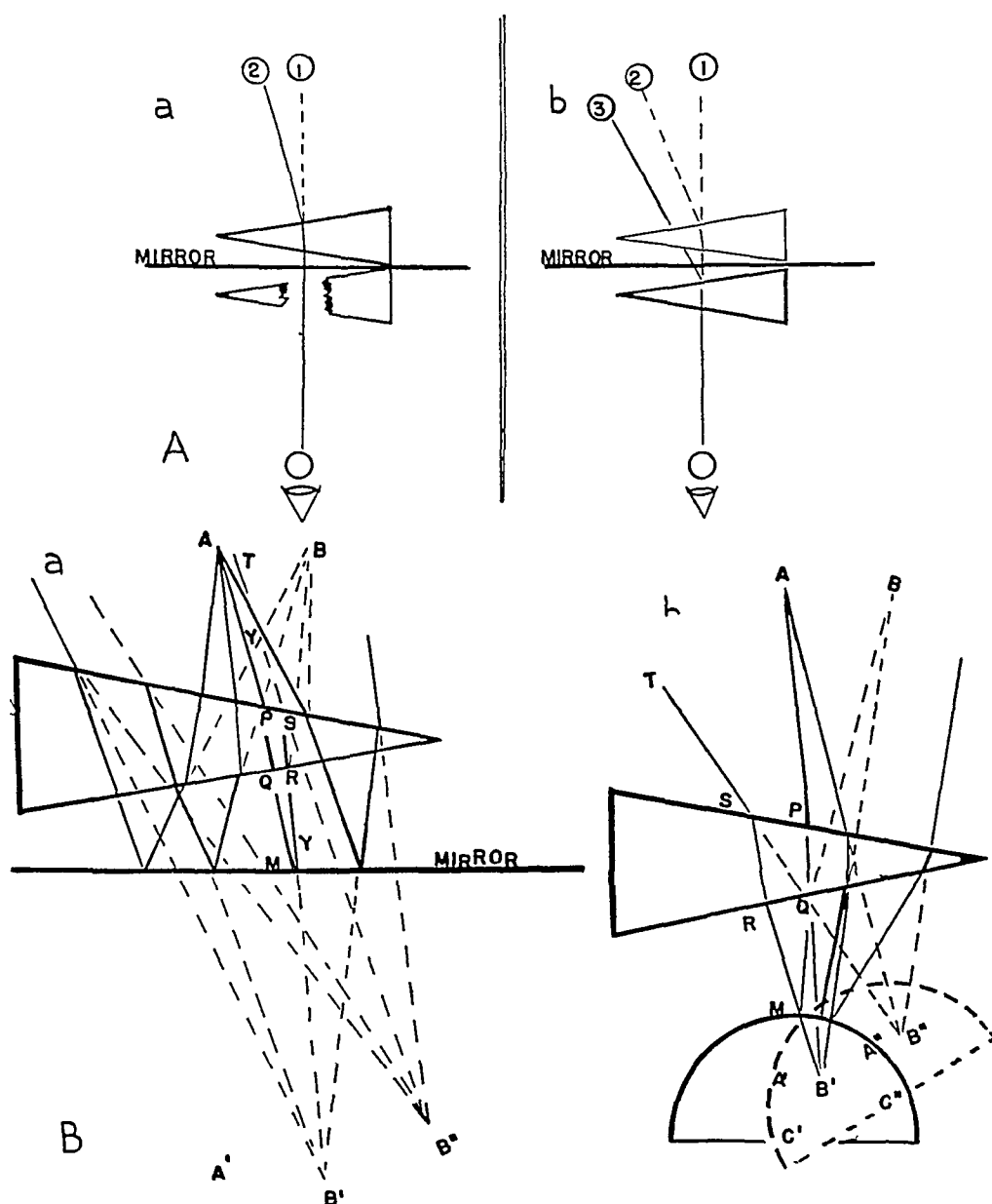


Fig 6—The prism reflex phenomenon. *A*, simple schematic drawing. (a) Displacement through image prism only. It was shown previously that with any mirror one has a reflection or an image. In this case one has a reflection of both prism and light. It is possible to exclude the image seen through the object prism (as shown in figure 3 *B*) and to study the displacement of light through the image prism alone. The effect as seen in the diagram speaks for itself. The light is displaced toward the apex.

(b) Displacements through object and image prisms. The observer looks through the object prism. In doing so, he sees the combined effects of the object and image prisms, respectively. He sees displacement of light from position 1 to position 2, as in the previous instance, by the image prism, and he also sees the additional displacement of the light from position 2 to position 3 by the object prism. What one sees in making a prism test is the displacement of the image to position 3. This represents the true strength of the prism, provided it is placed close to the cornea.

*B*, technical drawing as applied to (a) plane mirror and (b) convex mirror.

which the eye can accept, there is no difficulty when the image is being seen by the eye. The diagrams are drawn for a 20 D prism, i. e., one producing an angular deviation of about 11.5 degrees. (If  $\Delta$  is the power of the prism in diopters, then the angle of deviation is approximately  $\Delta/100$  radians, or  $1.8\Delta/\pi$  degrees.) For glass, the index of refraction of which is 1.53, this angle of deviation would correspond to a prism angle of about 21 degrees, as shown in the following formula

$n$  = index of refraction of  
glass, or 1.53

$$1 \Delta = 0.573^\circ \text{ (arc)}$$

Formula for using a 20 D prism

$$\frac{\Delta \text{ (in degrees)}}{n - 1}$$

$$\frac{20 (\Delta) \times 0.573}{1.53 - 1} = \frac{11.46^\circ}{0.53} = 21^\circ$$

The case of reflection from a plane mirror is shown in figure 6 B, a. The source of light is at point  $A$ . A pencil of four rays is shown, which, after passing through the prism, appear to come from point  $B$ . That is, the prism forms a virtual image of  $A$  at  $B$ . After reflection from the plane mirror, the rays appear to come from point  $B'$ , which is the virtual image of  $B$  formed by the mirror. After passing through the prism a second time, the rays appear to come from point  $B''$ , which is the virtual image of  $B'$  formed by the prism. Without the prism, an observer near  $A$  will see the image of the source at  $A'$ , with the prism interposed, he will see the image at  $B''$ . Tracing one of the rays ( $AP$ ) through in detail, one has the following. The ray  $AP$ , after passing through the prism, follows the path  $QM$ , which makes an angle,  $Y$ , with  $AP$ . After reflection, the path is  $MR$ , and after the second passage through the prism it is  $ST$ , which makes an angle,  $Y$ , with  $MR$ .

The total displacement of the image by the prism is easily found. If the distance from the light source to the mirror is designated as  $D$  and the distance from the prism to the mirror as  $d$ , one has approximately

$$AB = A'B' = (D - d) Y$$

$$B'B'' = (D + d) Y$$

and, adding the two equations,

$$A'B'' = 2 D Y$$

It is interesting that—at least to a first approximation—the displacement is independent of the position of the prism, but is directly proportional to the distance of the light from the mirror. The distance  $A'B''$ , which is the actual linear displacement of the image by the prism, is one which would be hard to measure experimentally except by some sort of parallactic arrangement.

The more important case of a convex spherical mirror is shown in figure 6 B, b. A pencil of three rays is shown, the middle ray being

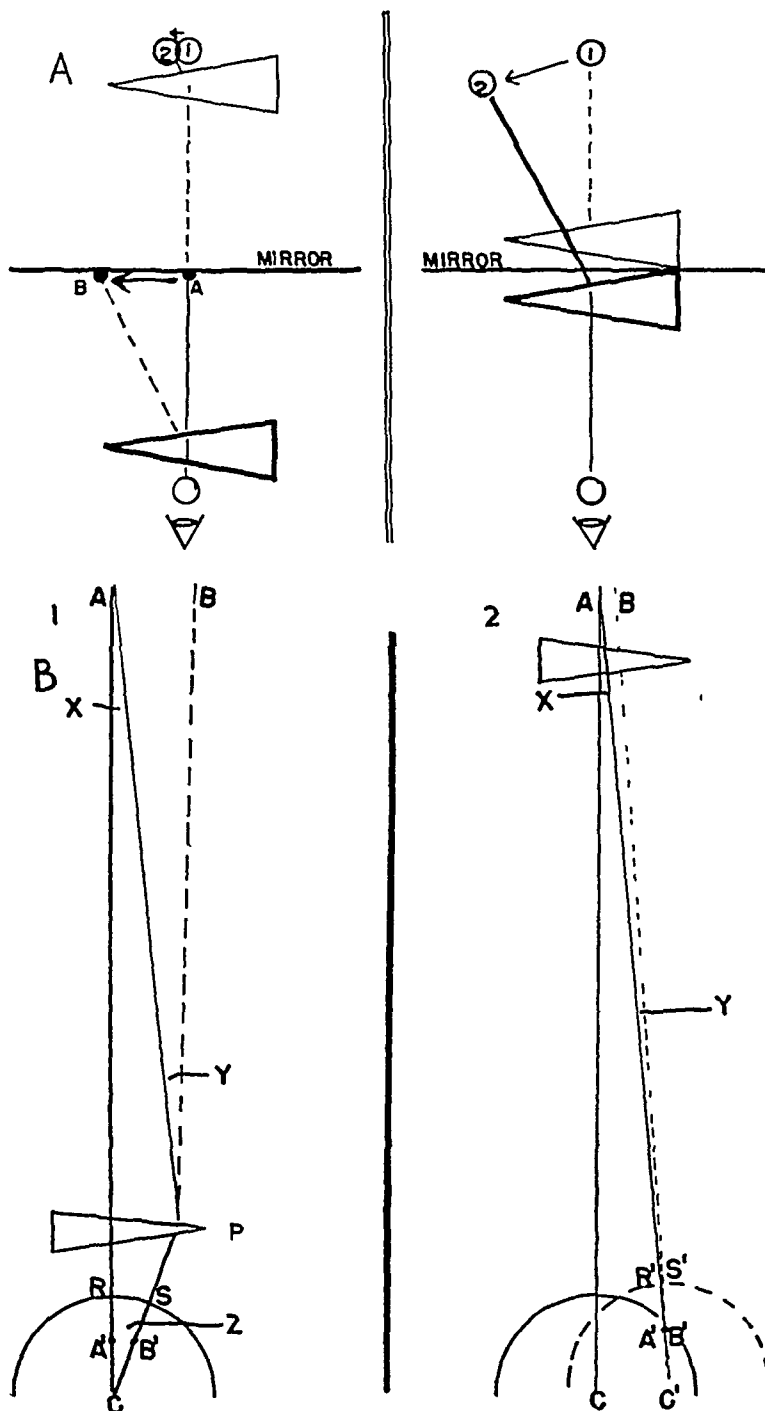


Fig 7—Diagrams showing how the distance of the prism from the eye affects prism power, as well as displacement of the corneal light reflex by prism

*A*, simple schematic drawing In this drawing, the prism is placed at two separate distances from the plane mirror—in one instance, at an appreciable distance from the mirror and near the test light, and in the other, close to the mirror In both instances the image prism assumes positions directly opposite the object prism In the case in which the prism is placed at an appreciable distance from the mirror, and close to the test light and the observer's eye, one notes a surface displacement of point *A* to point *B* (as in figure 8) This is comparable to seeing the eyeball itself appear shifted, as in the phorometer with the prism drawn away from the eyes However, since the light reflection is behind the cornea, the "reflex" seen through the mirror at position 1 without prism is shifted through but a small range to position 2, even though the surface displacement is considerable The displacement of the light reflex therefore operates inversely to that of the surface shift When the image prism is close to the image light, the surface displacement is maximal and the light displacement is minimal, when the object prism is close to the surface of the mirror, the light displacement is maximal and represents the true effectiveness of the prism

*B*, technical drawing, explained in the text



the one which strikes the mirror normally and after reflection retraces its path. As before,  $A'$  is the virtual image of  $A$ , formed by the mirror if the prism is not present,  $B'$  is the virtual image of  $B$ , which, in turn, is the virtual image of  $A$  formed by the prism,  $C'$  is the center of curvature of the mirror. The points  $A''$ ,  $B''$  and  $C''$  are the virtual images of the corresponding points  $A'$ ,  $B'$  and  $C'$  formed by the prism. An important difference between this case, of the convex spherical mirror, and that of the plain mirror is the fact that in this case one is interested not in the total linear displacement of the image but, rather, in the displacement of the image with respect to the mirror. The reason for this is that since the rays of light by which one sees the mirror also pass through the prism and are bent through the same angle as the reflected rays, one sees a virtual image of the mirror in the position shown by the dotted circle in figure 6  $B$ . The final result is that the apparent displacement of the image is  $A''B''$ , which is the same as  $A'B'$ , the displacement produced by one passage through the prism.

#### EFFECTIVENESS OF A PRISM WITH VARYING DISTANCES FROM EYE

It will be noted that as the prism is moved away from the eye and closer to the test light, the eye and the surrounding brow appear to move toward the apex of the prism. This serves to reduce its effective power. The displacement of the light reflex by the prism becomes less as it is moved away from the eye, even though the eye and its surrounding structures, such as the eyelids, appear to move with the rotation of the prism. As the prism is moved closer to the eye, it appears to return (in the direction of the prism base) to its natural position, and when the prism is close to the eyeball, one notes no apparent displacement of surface structures with changing strength of prism. The only effect in this apposed position is in change in the position of the light reflex with variation in the strength of prism. In this apposed position the effectiveness of the prism is maximal.

Figure 7  $B$  is a simplified diagram showing only two rays and omitting the prism. The rays shown are  $AA'C$ , which strikes the mirror normally if the prism is not present, and  $APB'C$ , which strikes the mirror normally after passing through the prism, to left of  $P$  in diagram. The effect of the prism is indicated by the deviation of the ray through angle  $Y$  at point  $P$ . What is wished is an expression for the displacement of the corneal reflex at the surface of the cornea. In figure 7  $B$  this is the distance  $RS$ . If  $D$  and  $d$  have the same meanings as before, then when  $Y$  is small,  $AC = D$ , and  $PC = d$ , approximately. Applying the "sine law" to triangle  $APC$ , one has

$$\sin X = (d/D) \sin Y$$

If the angle  $Y$  is reasonably small, one can get a fairly good approximation by setting the sines of the angles as equal to the angles themselves. Doing this, one has

$$X = (d/D) Y$$

and, since  $X = Y - Z$ ,

$$Y - Z = (d/D) Y$$

One now has for the distance  $RS$

$$\begin{aligned} RS &= r Z \\ RS &= r (1 - d/D) Y \end{aligned}$$

If the distance from the mirror to the prism is small as compared with the distance from the light to the mirror, then  $d/D$  is small as compared with 1, and the displacement  $RS$ , is approximately  $r Y$ . In other words, if the prism is placed close to the eye, the displacement of the corneal reflex along the surface of the cornea is simply the radius of curvature of the cornea multiplied by the angle of the deviation produced by the prism, this angle being measured in radians, and being equal to the power of the prism, expressed in diopters, divided by 100. On the other hand, as the prism is moved closer to the light,  $d/D$  approaches 1 and  $Z$  approaches 0.

If point  $S$  is the center of the cornea, the rays of light which pass through the cornea will be brought to a focus on the center of the retina. That is, when the reflex is brought to the center of the cornea, the rays will be along the visual axis of the eye. If the prism is close to the eye, the angle of deviation of the eye is exactly the angle of deviation of the prism required to correct it.

In conclusion, as the prism is moved toward the light, the eye (mirror) moves toward the apex of the prism, since the displacement of the mirror by the prism is directly proportional to the distance from the mirror to the prism. At the same time, the displacement of the reflex on the mirror becomes smaller, since the angle  $Z$ , which is approximately  $(1 - d/D) Y$ , becomes smaller as  $d$  becomes larger and is 0 when  $d = D$ .

When the prism is moved toward the eye, the image of the eye moves toward the base (of the prism), owing to the fact that as the distance from prism to eye is decreased the displacement of the eye becomes smaller and the eye moves toward its actual position, i. e., toward the base. At the same time the displacement of the reflex on the mirror becomes larger, since  $Z$  increases as  $d$  increases.

#### PRACTICAL CONSIDERATIONS IN THE PRISM REFLEX TEST

On the basis of the foregoing problems, one must conclude that the prism reflex test is closely related to established methods of prism testing. Because it is objective, it simplifies the clinical use of the

prism The position of the examiner's eye exactly behind the test light and the placement of the prism close to the eye are important if one is to obtain the optimal value of the prism Thorington,<sup>5</sup> Hardy<sup>6</sup> and others have shown that clumsy placement of a prism before a patient's eye will yield variable readings for a particular prism strength The reports are valuable only from an academic standpoint because one would not think of holding a prism in the extreme positions which these authors have shown as leading to greatest errors They mention the split beam position, the Prentice position and the reverse Prentice position as being nearest the true value of the prism reading However accurate one may be in the placing of the prism before the eye, one cannot be too exact in attaining either of the aforementioned ideal positions A commoner reason for error which these authors failed to mention was the abnormally large distance of the rotary prisms from the eyes in the case of the phorometer Because of the presence of the forehead rest and the frame structure between the prisms and the eyes, producing a separation averaging 4 to 5 cm, one can expect gross inaccuracy in prism readings If one holds the test light at a distance of 25 cm from the eyes, the effectiveness of the prism is reduced between 16 to 20 per cent, so that a prism reading of 30 $\Delta$  would really indicate 25  $\Delta$  or less For that reason, I prefer the hand rotary prism, such as the Hughes type, which one can place close to the eyes, and which therefore would not affect the numerical reading of the prism to any notable extent

Another disadvantage of the phorometer is the apparent shift of the eyeball medially as a base-out effect is produced Considering that the prism may be as much as 5 cm from the eyes, one would expect displacement of an image or an apparent eye and face displacement of 0.5 mm for each prism diopter With a prism of 30  $\Delta$  base out, the apparent displacement of the stationary cornea would be 1.5 cm, and with 60  $\Delta$  it would amount to 3 cm, in which case the cornea would be well hidden behind the framework of the phorometer (fig 8) Here, too, it is the construction of this instrument and the large distance of the rotary prisms from the eye which produce such an effect This phenomenon is entirely distinct from effective prism power, which was previously discussed The hand rotary prism placed close to the eyes would obviate such a shortcoming

Bearing in mind the aforementioned reasons for error with the prism method, as well as the fact that the prism is more accurate in

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5 Thorington, J Prisms Their Use and Equivalents, Philadelphia, P Blakiston's Sons & Co, 1913

6 Hardy, L H Clinical Uses of Ophthalmic Prisms (Metric), Arch Ophth 34 16-23 (July) 1945

the lower values and for lesser degrees of squint, the real value of the prism lies in its ease of handling, rather than in reliability in readings. At best, I regard a prism reading as an approximation. In my experience, the angloimeter<sup>6a</sup> has proved the simplest and most accurate method of measuring ocular deviations, because it is based on the cover test and on simple adjustment of the lighted target to any position of a deviated visual axis under controlled conditions.

In order to judge the true position of the corneal light reflex, the pupil should not be dilated by any mydriatic. With a small pupil one can make an accurate note of an angle gamma. With a greatly dilated pupil one may be confused as to whether such a light reflex is central or off center.

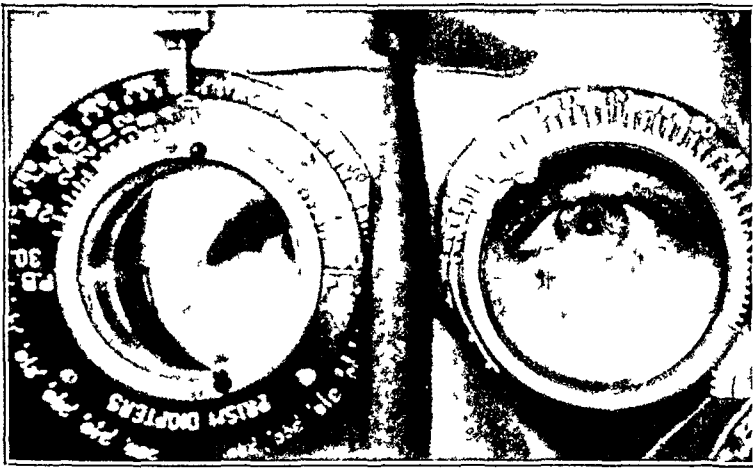


Fig 8—Photograph showing how the phorometer reduces the effectiveness of its prisms.

The phorometer has a definite disadvantage over the simple hand rotary prism because of the excessive framework, which increases the distance between the eyes and the prism. In order that any prism may be effective, it should be placed as close to the eyes as possible. Note how the right eye is displaced inward and its cornea is hidden from view by the 30 $\Delta$  base-out prism. This means that the effectiveness of this mechanism is zero because the eye is completely hidden from view.

The prism reflex test is dependable and satisfactory at a working distance of 13 inches (33 cm) or less. At the near ranges the examiner can keep his eye directly behind the test light and in direct line with the patient's pupil.

For the 20 foot (6 meter) distance, the observation of the corneal light reflexes cannot be controlled as readily as for the 13 inch range, because the test light at that distance is too faint to register a visible corneal light reflex. Moreover, the examiner's head would be in the direct path of the light beam. By using a brighter light, say a 10,

<sup>6a</sup> Krinsky, E. The Cardinal Anglometer, Arch Ophth **26** 670-674 (Oct) 1941

25 or 40 watt Mazda lamp, for the 20 foot distance, and a magnifying mirror held obliquely in front of the patient's forehead, as in my stereoscope,<sup>7</sup> I have been able to observe the corneal light reflexes clearly

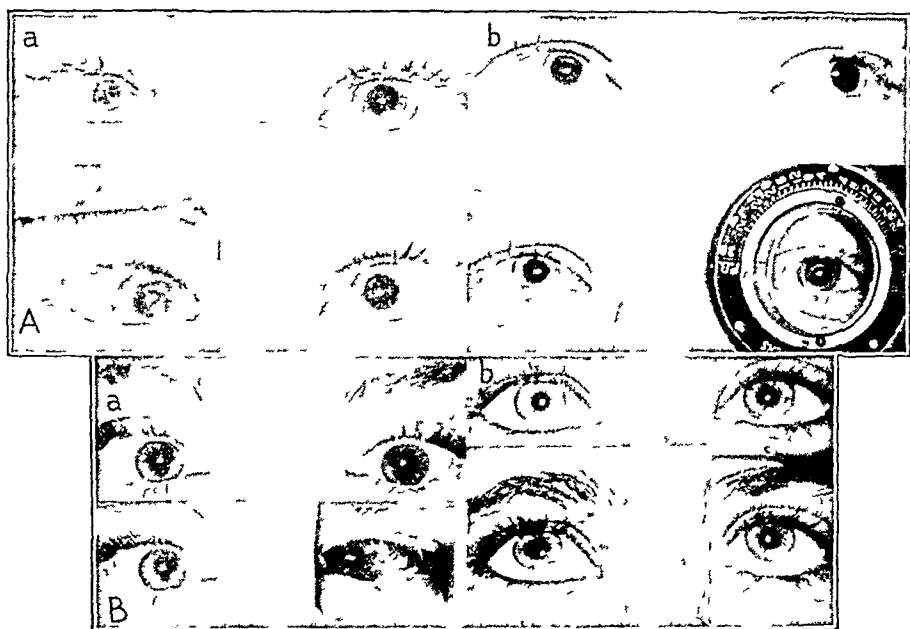


Fig 9—Photographic demonstration of clinical applications of the prism reflex test

*A*, measurement of heterotropia or manifest squint (a) Convergent squint In manifest squint the right eye is deviated inward As a result, the corneal light reflex is displaced outward A base-out prism of sufficient strength to restore the light reflex in that eye to its fixational position represents the measure of the deviation A supplementary cover test will confirm the correctness of the prism reflex test

(b) Divergent squint The left eye is deviated outward and the light reflex is displaced inward A rotary prism to produce the effect of a  $30\Delta$  base-in prism (as in the illustration) also restores the light reflex to a central, or fixational, position without changing the position of the eyeball itself This serves as measure of the deviation

*B*, measurement of prism vergence in binocular fixation (a) Prism convergence First, eyes straight with the light reflexes in their fixational positions A base-out prism ( $40\Delta$ ) is then placed over the left eye, and the reflex is still in a fixational position because that eye has converged to overcome the displacement that would otherwise be produced by the prism The result is the maintenance of binocular fixational reflexes with binocular single vision

(b) Objective diagnosis of heterophoria—exophoria A “strong” base-down prism is placed over the left eye, as in the familiar prism dissociation, or von Graefe, test, except that the examiner observes the corneal light reflexes at the same time One now sees that as a result of the prism the light reflexes are no longer fixational in both eyes The light reflex is in fixational position in the left eye but in the right eye it has shifted downward and inward, the downward component is due to the prism, and the inward component is due to a latent deviation of the outward component, or exophoria The image response is crossed vertical diplopia, corresponding to the positions of the light reflexes Measurement consists in transforming this to a true vertical diplopia by supplementing with added base-in prism, which moves the light reflex from an inward to a midline position

7 Krinsky, E Modification of the Brewster Stereoscope for Clinical Requirements, Arch Ophth 26 808-815 (Nov) 1941

through the mirror while standing behind the patient and, at the same time to perform the cover test satisfactorily

A small test light at the 20 foot distance would subtend too small an angle to register a light reflex of proper size. One may object to a larger test light because it is too large for critical fixation. In my experience, a small 20 foot test light should be reserved for those who depend on the Maddox rod test to provide subjective information based on a fine streak image. The small 20 foot test light can be dispensed with for the prism reflex test if one is seeking objective information.

In making a prism test, the examiner should look through the object prism rather than above it. As shown previously, the displacement of the light reflex by both the object prism and the image prism represents the power of a particular prism. Instinctively, however, the examiner looks through the object prism without necessarily realizing the true importance of such direct inspection.

#### CONCLUSIONS

- 1 The cornea is a convex spherical mirror. Hence, the corneal light reflex is an erect virtual image at the principal focus of the sphere.

- 2 The corneal light reflex is a misnomer because it is subcorneal in position and is 3 to 4 mm behind the anterior surface of the cornea. It is technically a reflection.

- 3 Rotation of a mirror on its edge, or vertical axis, produces a displacement of the lighted image similar to that which one would expect with displacement of the image by a prism.

- 4 Such a reflex image can be restored to a neutral position by corrective prism. Moreover, the visual axis, which is bent through rotation of the mirror, is also apparently rectified by such prism.

- 5 The corneal light reflex is, strictly speaking, not a Purkinje image but a light reflection, which one would find in any convex spherical mirror.

- 6 The prism displaces the corneal light reflex toward its apex in an eye which remains stationary. The amount of prism correction corresponds accurately to the numerical strength of the prism only when such prism is placed close to the eye.

- 7 The size of the corneal light reflex is important for critical testing. A large reflex may prove confusing.

- 8 The true measure of the strength of a prism depends on the examiner's looking through the prism rather than above or below it. It is a combination of object prism and image prism which registers

the true value of the prism. If one looks above the prism, one is apt to see only a partial displacement of the light reflex, resulting from the image prism only. In making a routine prism test, one instinctively looks through the prism because it covers so large a surface of the eye.

9. The distance of a prism from the eye has an important bearing on its strength. Undue separation of the prism from the eye reduces its effectiveness by as much as 20 per cent. For that reason, the phorometer is inaccurate. The hand rotatory prism or prism rack or single prisms can be handled more effectively.

Miss Sonia Mitchell assisted in the construction and technical description of figure 6 *B*, and Dr Edwin W. Bechtold reviewed the data after completion of the manuscript.

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# LIGAMENT OF LOCKWOOD IN RELATION TO SURGERY OF THE INFERIOR OBLIQUE AND INFERIOR RECTUS MUSCLES

WALTER H FINK, M D  
MINNEAPOLIS

**A**N ANATOMIC study of the suspensory ligament of the eye, (ligament of Lockwood) based on a series of dissections, is presented. Certain phases of the anatomic structure of the ligament which seem to be of importance in the management of abnormalities of the inferior oblique and inferior rectus muscles are presented.

The suspensory ligament, as described by Lockwood, consists of a blending of the sheaths of the inferior oblique and inferior rectus muscles to form a special thickening of the fascial structure. The lateral expansion of this sheath extends upward laterally and medially to join the sheaths of the lateral and medial rectus muscles, thereby gaining indirect attachment to the orbital margin. There is thus formed a continuous band about 0.1 inch (0.25 mm) thick beneath the globe, which supports it like a hammock.

Generally speaking, the ligament is thought of as a "suspensory hammock" which functions as a support to the eyeball. Insufficient emphasis has been placed on its other functions, which have to do with its relation to the inferior oblique and inferior rectus muscles. From a review of the literature, supplemented with a series of dissections, it is apparent that, in addition to the suspensory action, the ligament has a definite function in promoting a smooth, integrated action of these muscles. In the region of the inferior oblique and inferior rectus muscles, the structure of the ligament becomes modified, thus enabling it to perform certain specialized functions.

The investigation emphasized three important modifications of the ligament in its relation to these extraocular muscles. First, and perhaps most important, is the modification of the ligament at the point of crossing of the two muscles. Second is the modification of the ligament which serves as a sheath to the inferior oblique muscle lateral to the point of crossing. Third is the modification of the ligament which functions as a check ligament to the inferior oblique muscle, and, in addition, acts in conjunction with the inferior oblique muscle to serve as a check ligament to the inferior rectus muscle.

The most important modification of the suspensory ligament is found

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at the point of crossing of the inferior rectus and the inferior oblique muscle. Various descriptions of this anatomic structure are found in the literature, but little emphasis has been placed on the variations which may be present in this highly specialized area, and insufficient stress is placed on its possible clinical importance.

A study of anatomic material reveals that a firm union exists between the inferior oblique and the inferior rectus muscle. This is produced by a fusion of the fascial sheaths of these muscles at the point of crossing. The fascial sheath on the under surface of the inferior rectus muscle becomes definitely thickened a few millimeters before it reaches the inferior oblique muscle. At the point where the muscles cross, this thickened fascia comes in contact with a similar thickening of the fascia

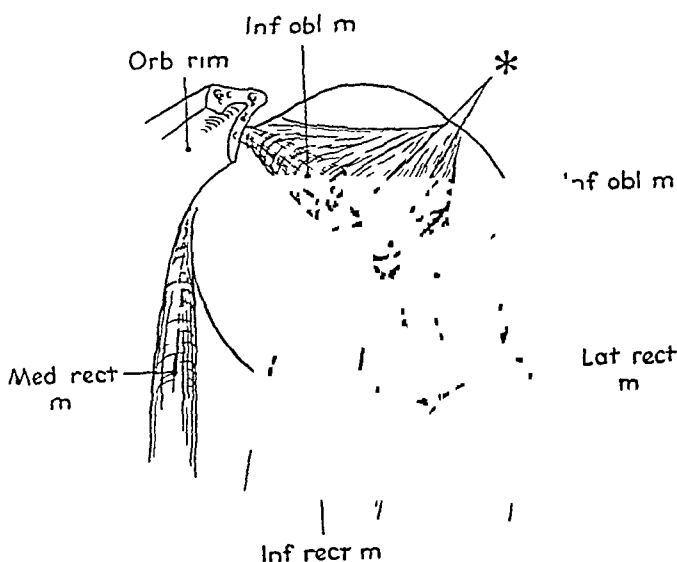


Fig 1—Crossing of the inferior oblique and the inferior rectus muscle as seen from below. The inferior oblique muscle is severed and turned laterally, showing a firm adhesion between the fascial sheaths of the two muscles. The asterisk indicates short, thick adhesions between the two muscles, which would cause practically complete fusion between the sheaths, resulting in little, if any, independent action of the two muscles.

covering the inferior oblique muscle. A fusion is brought about by numerous fascial bands which pass from one fascial sheath to the other.

Study of a series of specimens revealed that the degree of fusion between the fascial sheaths of these muscles is variable. Some specimens showed a firm union, which seemed to be a complete fusion of the fascial sheaths (fig 1). Others showed a very loose fusion, with but a few bands of fibrous tissue connecting the two fascial sheaths, and no difficulty was experienced in separating them (fig 2). Between these two types there was a series of specimens in which a fairly firm union existed and the fusion of the sheaths was moderate in degree. In these specimens

the fascial strands, although firmly uniting the two muscle sheaths, did not produce their complete fusion

The degree of independent movement of each muscle was in proportion to the degree of fusion of the fascial coverings of the two muscles. In specimens showing a firm union, there did not seem to be any apparent independent movement of the two muscles, and they gave the impression of a solidly fused structure. In specimens with loose fusion, the independent movement of the two muscles was definite. As would be expected, the specimens between these extremes showed variable amounts of movement, and the movement was in proportion to the degree of fusion present. The majority fell into the latter category.

It could be demonstrated that in the region where the muscles crossed the thickened fascial covering of the muscles was firmly adherent.

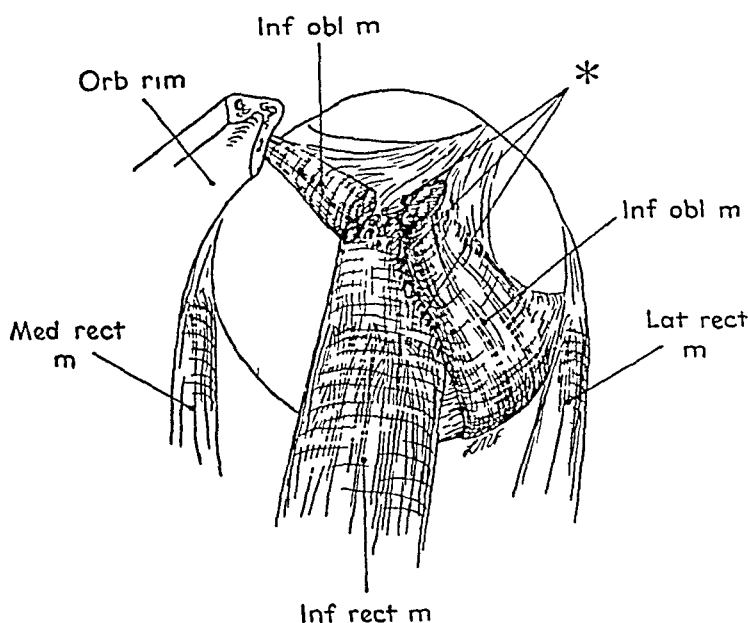


Fig 2—Crossing of the inferior oblique and the inferior rectus muscle as seen from below. The inferior oblique muscle is severed and turned laterally, showing loose adhesions between the fascial sheaths of the two muscles. The asterisk indicates long, delicate, loose bands of fibroelastic tissue, permitting considerable independent action of the two muscles.

to the muscle tissue. Whereas the outer layer was largely made up of circular fibers, the inner layer, which was in contact with the muscle tissue, had fibers which were mostly longitudinal. The inner layer was apparently continuous with the internal perimysium of the muscle and caused the muscle fibers to be firmly united to the fascial covering of the muscle.

It is obviously impossible to compare exactly prepared anatomic material with a similar structure in the living tissue. Anatomic material should, however, provide a basis for comparison of different degrees of union, because this variable degree of fusion of the structures should have much the same relation as in the living tissue.

From a clinical standpoint, it would seem that because of such an intimate fusion of the two muscles, any surgical manipulation of these muscles should be evaluated with this anatomic fact in mind. Such a variation in degree of independent action of the muscles should to some degree influence the functioning power of the muscles. The influence should be especially evident when an operation is performed on the muscle, particularly at the origin of the inferior oblique muscle. Operation at the origin of this muscle should produce variable results because of the variations in the degree of fusion at the point of crossing to the two muscles. It is logical to assume that a firm fusion between the muscles should lessen the effect of a tenotomy at the origin, more than would a fusion of less degree. One may conclude, herefore, that in surgical treatment of the inferior oblique, the insertion, rather than the origin, of the muscle is the logical point for the surgical approach, because more definite results may be anticipated.

The degree of fusion of the fascial sheaths at the crossing of the muscles may in a measure influence, likewise, the result when operation is performed on the inferior rectus muscle, because the fascial structure at this point likewise influences the action of this muscle.

One is tempted to speculate that a pronounced variation in the arrangement of the fascial tissues at this point might influence the physiologic action of these muscles to such a degree that clinical results commonly referred to as paresis or overaction of one or the other muscles would be produced.

It should be kept in mind that in operations on the inferior oblique muscle, such as a recession, the new point of attachment must not deviate from the plane of action of the muscle. The fixed position of crossing of the muscles demands this in order that the muscle may function efficiently. The question of the constant location of this point of crossing does not seem to be significant. The measurements taken in 40 specimens showed much the same relation to the eyeball.

The second anatomic consideration of the suspensory ligament of the eye is the modification of the ligament which forms a sheath for the inferior oblique muscle lateral to the point of crossing. As was true in the case of the sheath at the point of crossing of the muscle, the sheath in this area also had two layers, an outer layer with circular fibers predominating, and the inner layer, with longitudinal fibers predominating. The inner layer was continuous with the muscle tissue, being united with bands which blended with the perimysium of the muscle. These bands are of special significance, for they form an intimate connection between the muscle tissue and the muscle sheath, and at

operation it is occasionally necessary to separate the muscle from its sheath in order to obtain a satisfactory result

The nerve and blood supplies to the muscle perforated the sheath on the posterior edge just after it crossed the inferior rectus muscle. Near the insertion, the muscle sheath fanned out anteriorly to fuse with the sheath of the lateral rectus muscle and posteriorly to fuse with the fascial sheath surrounding the optic nerve (fig 3). In this posterior area, the fascia was perforated by the ciliary vessels and nerves.

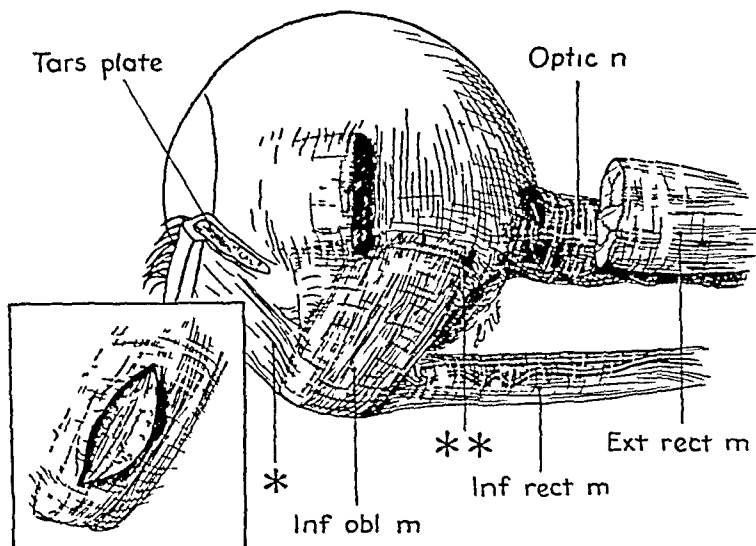


Fig 3—Lateral view of the eye, showing the lateral half of the inferior oblique muscle (after its crossing with the inferior rectus). The drawing shows the extensions of the membranous sheath covering the inferior oblique muscle anterior to the sheath of the lateral rectus muscle and posterior to the fascia surrounding the optic nerve. It is particularly important that these fibrous extensions be severed in doing operative work on the inferior oblique muscle.

The single asterisk indicates the fascial sheath extending forward to the tarsal plate, which acts as a check ligament to the inferior oblique muscle. The double asterisk indicates the posterior extension of the sheath of the inferior oblique muscle to fuse with the sheath of the optic nerve.

The small insert illustrates a portion of the inferior oblique muscle with its fascial sheath. In this drawing, a portion of the sheath has been cut to permit a view of the fibrillae which pass from the inner surface of the sheath to the perimysium of the muscle, thus forming a firm union between the sheath and the muscle.

It is obviously important to sever all of this sheath, as well as the insertion of the muscle, in order to secure the desired surgical effect. To sever only the muscle and do a recession while the sheath remains intact at the posterior edge would tend to nullify the effect desired. In severing the sheath, it is important to remember its relation to the ciliary vessels and nerves in this region—the fovea, which is just above the posterior tip of the muscle, the vortex vein, and the artery and nerve.

supplying the muscle (fig 4) It is well to also bear in mind the firm union of the fascial sheath and the muscle

The third anatomic consideration of the suspensory ligament of the eye is the modification, which acts as a check ligament to the inferior oblique muscle Motais<sup>1</sup> was the first to demonstrate this function of the suspensory ligament, and Maddox<sup>2</sup> gave the following description

" a fibrous bundle, derived in part from the fibres of the sheath of the inferior rectus, in part from the sheath of the inferior oblique muscle, which leaves the anterior border of the inferior oblique about 8 or 10 millimeters from its orbital origin, and from thence courses obliquely outwards and forwards It forms an obtuse angle of about  $120^{\circ}$  with the check ligament of the inferior rectus muscle With the inferior oblique it forms an angle of about  $110^{\circ}$  Its length is from 10 to 12 millimeters, and it is inserted into the lower outer angle of the orbit,

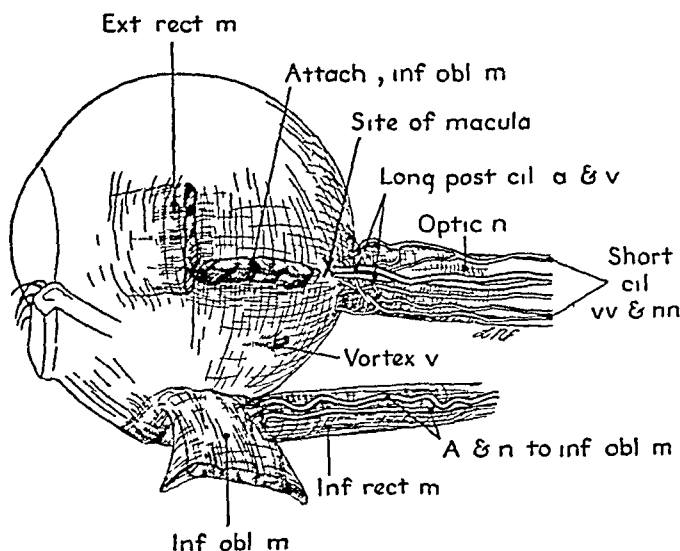


Fig 4—Lateral view of the eyeball, in which the inferior oblique muscle is cut and turned downward to show its line of insertion to the sclera The figure although diagrammatic, shows accurately the relations of the various structures as observed in anatomic specimens

The vortex vein is usually seen 10 to 12 mm below the posterior end of the attachment of the inferior oblique muscle and immediately under the posterior border of the muscle The diagram attempts to illustrate the oblique position of the vortex vein as it enters the sclera Note the relation of the macula, ciliary vessels and nerves to the posterior tip of the insertion of the inferior oblique muscle The artery and nerve enter the inferior oblique muscle just lateral to the point where this muscle crosses the inferior rectus muscle

4 or 5 millimeters behind the orbital margin, about midway between the external check ligament and the origin of the inferior oblique

This bundle is mostly pearly looking, the most purely fibrous of all the aponeurotic lamellae of the orbit.

1 Motais, E Recherches sur l'anatomie humaine et l'anatomie comparee de l'appareil moteur de l'oeil, Arch d'opht 4 532-537, 1885

2 Maddox, E E Tests and Studies of Ocular Muscles, Bristol, J Wright & Co, 1898, p 32

Its breadth varies at different parts of its course in the middle, 2 or 3 millimeters, at its muscular insertion, 7 or 8 millimeters, at its bony insertion, 5 or 6 millimeters. It presents, therefore, the shape of two triangles united by their apices. Together with the inferior oblique itself, it forms a kind of musculo-aponeurotic loop, the two ends of which are inserted near the orbital margin, one at the outer angle, the other at the inner angle. The check ligament of the inferior rectus muscle embraces the middle portion of this loop, so that when the inferior rectus begins to contract, its check ligament stresses the loop.

Duke-Elder<sup>3</sup> mentioned the presence of a fascial strand running laterally and backward to the orbital floor. Others have expressed doubt, however, as to the existence of a definite check ligament of the inferior oblique muscle. Whitnall<sup>4</sup> pointed out that in his dissections he found

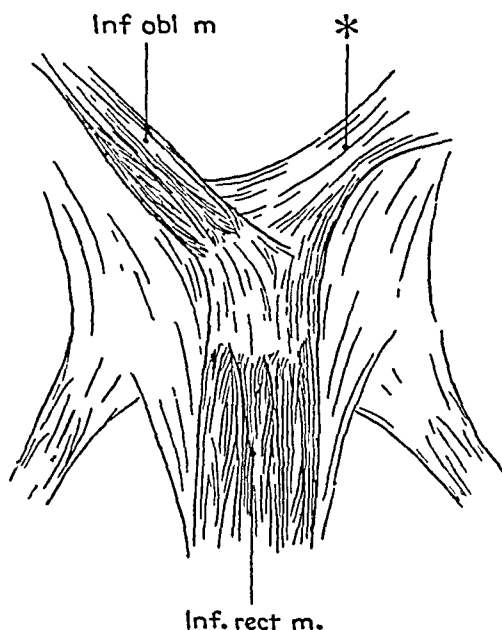


Fig 5—Diagram taken from the work of Motais. The asterisk illustrates the arrangement of the check ligament of the inferior oblique muscle. According to Motais, this check ligament, together with the inferior oblique muscle, has a check action on the inferior rectus muscle. The arrangement is described as a Y-shaped affair. With such an arrangement, it is obvious that a tenotomy of the inferior oblique at its origin would affect the check action on this muscle and likewise affect the check action on the inferior rectus muscle.

but 1 instance in which "a strand" would be reasonably possessing any such action." Fuchs<sup>5</sup> stated that "the inferior oblique has no check ligament, its place being taken by the ligament attached to the reflected tendon of the superior oblique."

3 Duke-Elder, W. S. Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1933, vol. 1, p. 181.

4 Whitnall, S. E. Anatomy of the Human Orbit, New York, Oxford University Press, 1932, p. 297.

5 Fuchs, E. Textbook of Ophthalmology, translated by A. Duane, ed. 7, Philadelphia, J. B. Lippincott Company, 1923, p. 58.

With such a difference of opinion, the question arises as to the exact status of the check ligament of the inferior oblique. It would seem that the ligament must exert some check, but it is doubtful whether it is the well defined mechanism described by Motaïs.

In the present series of dissections, an effort was made to answer the question. After careful investigation, it seems apparent that no such mechanism as that described by Motaïs was evident in this series of specimens. It could be demonstrated that in the location described there were present bands of fascia in various numbers, and arranged in such a manner that they could act in the capacity of a check ligament to the inferior oblique muscle. Most of these strands blended posteriorly with the fibrous sheath of the inferior oblique, and anteriorly seemed to be attached to, or blended with, the septal membrane of the orbit, thus

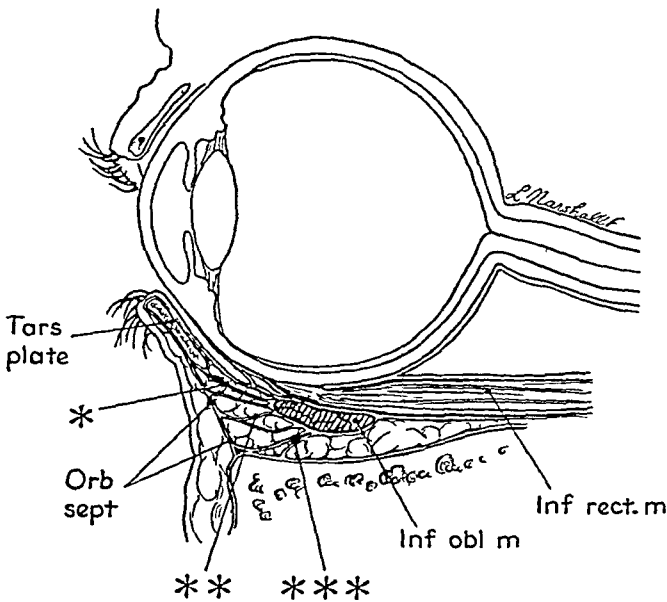


Fig 6—Vertical section of the check ligament of the inferior oblique muscle. The fascial covering of the inferior oblique muscle extends forward, having extensions to the lower cul-de-sac, the lower tarsal plate and the septum orbitale, and a few strands to the periosteum on the floor of the orbit.

The single asterisk indicates fibrous bands extending to the tarsal plate, the double asterisks, fibrous bands extending forward to the septum orbitale, and the triple asterisks, fibers extending to the periosteum on the floor of the orbit. These are usually not direct extensions but are made up of the fibrous network which surrounds fatty tissue.

becoming indirectly attached to the orbital rim. Other strands seemed to blend with the supporting structure surrounding the fatty tissue, and were thus indirectly attached to the periosteum of the floor of the orbit immediately behind the orbital rim (fig 6). In no case was a definite ligament present, as described by Motaïs, instead, the arrangement appeared rather as a broad meshwork of fascial fibers, which in some instances was compact and had the appearance of an extension of the muscle sheath.

This fascial membrane in several cases was definitely more compact near the point of crossing of the muscles and formed a firm band between this area and the orbital septum immediately anterior to it (fig 7). Although the arrangement was not that described by Motais it is reasonable that such a structure could act as a check ligament to the inferior oblique muscle and, through its action with the inferior oblique, as check ligament to the inferior rectus muscle.

As in the case of the other check ligaments, this structure undoubtedly is a factor in promoting more efficient action of the inferior oblique muscle. Motais expressed the belief that it acts not only as a moderator of the action of the inferior oblique, but also as a "pulley of reflection." By this he must have meant that when the muscle contracts the ligament

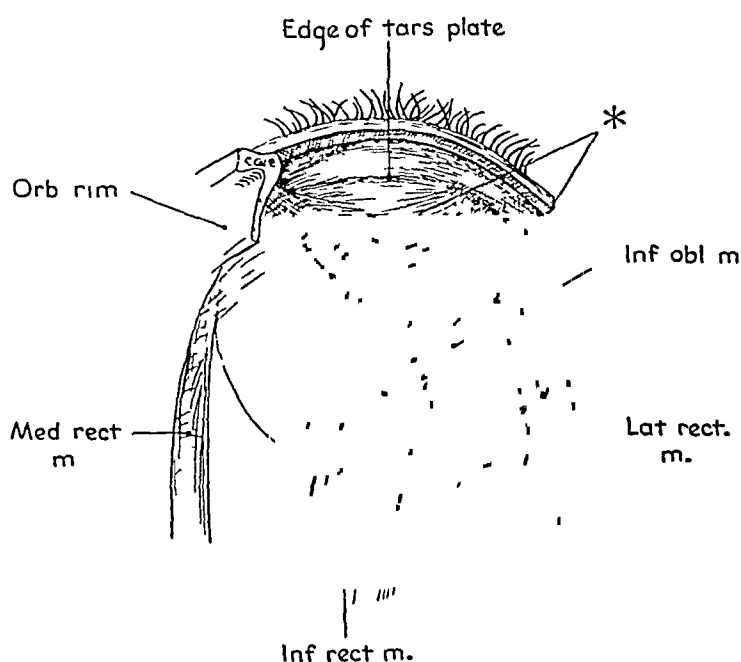


Fig 7—Fascial arrangement covering the inferior oblique and inferior rectus muscles as seen from below

The asterisk illustrates how the fascial covering of the inferior oblique muscle is continued forward and fuses with the lower edge and with the body of the tarsal plate. It will be noted that in the region of the crossing of the muscles the membrane is denser and takes on somewhat the arrangement described by Motais, although it is not so sharply defined. By this specialized arrangement the ligament of Lockwood serves as a check ligament to the inferior oblique muscle and, in conjunction with this muscle, acts as a check ligament to the inferior rectus muscle.

slightly bends the muscle by drawing its middle part outward, so as to make its traction on the eye a little less oblique.

A surgical approach to the inferior oblique muscle should avoid interference with the action of this structure. Tenotomy performed on the insertion would be less likely to interfere with its action than would an operation at the origin of the muscle.



The check ligament of the inferior oblique muscle very likely plays an important role in conjunction with the inferior oblique muscle to act with the check ligament to the inferior rectus muscle. The check ligament of the inferior rectus apparently has no direct insertion into the margin of the orbit, but acts only through the aforementioned structure, one limb of which is formed by the inferior oblique muscle and the other by the check ligament of the same muscle. As stated by Motais,

The check ligament of the inferior rectus has, therefore, for its orbital insertions, the tendon of the inferior oblique muscle, and the check ligament of the same muscle like the two limbs of a Y

If such an anatomic arrangement is present, it is evident that tenotomy of the inferior oblique at its origin will also disrupt a balanced check action on the inferior rectus muscle and thus cripple the normal action of that muscle. This factor alone should cause one to avoid any surgical manipulation of the inferior oblique muscle at its origin.

It is also important to emphasize that an extension of the suspensory ligament of the eye also is attached to the lower tarsal plate and cul-de-sac and tends to hold them in place. Surgical manipulation of the inferior rectus should be such that this extension is not disturbed.

#### CONCLUSION

The suspensory ligament of the eye (ligament of Lockwood), in addition to being a "suspensory hammock," is of importance to the clinician because of its specialized functions in relation to the inferior oblique and the inferior rectus muscle.

From an anatomic standpoint, the surgical approach to the inferior oblique muscle should be at its insertion. Operation at the origin of the inferior oblique would produce more uncertain results because of the variable degree of fusion with the inferior rectus muscle at the point of crossing and would also tend to disturb the action of the check ligament, which is essential to an efficient action of the muscle. Operation at the origin of the inferior oblique muscle would also weaken and distort the check action on the inferior rectus muscle, an action which is dependent on a balance of pull between the inferior oblique muscle, from its crossing to its origin, and the check ligament of the inferior oblique muscle.

In operation at the insertion of the inferior oblique, one should consider not only the insertion of the muscle but also the insertion of the muscle sheath and the important structures passing through it. In recession, the muscle should be reattached in the line of action.

It is important, therefore, in contemplating any surgical procedure on the ocular muscles, to evaluate the step with the anatomic facts in mind. An ill advised surgical procedure not only may be ineffectual but may also cripple the action of more than one muscle.

## ABSTRACT OF DISCUSSION

DR MAYNARD WHEELER, New York We are greatly indebted to Dr Fink for making this study. Most physicians think that they are too busy to go back to the cadaver for review, not to mention new discoveries. Fortunately, there are a few staunch members of the medical profession who are willing to make this sacrifice. The recent trend in surgery of the inferior oblique has been to shift attention from the origin to the insertion of this muscle. Dr Fink has now placed this on a rational basis. However, at the same time, he has added to the already formidable list of hazards to be encountered in this region. He has explained the highly variable results that all have experienced in doing myectomies near the origin of the inferior oblique muscle. No doubt, in those embarrassing cases in which some overaction of this muscle persists after a myectomy a firm union between the inferior oblique and the inferior rectus muscle existed. Dr Fink hinted at the possibility that this firm union might explain the overaction of the inferior oblique muscle which so frequently accompanies lateral squint. I wish that he would speculate further on this important point. If the two inferior muscles are firmly adherent to their sheaths and the sheaths are closely united, it is hard to see how these somewhat antagonistic muscles function properly and independently.

Dr Fink mentioned that Lockwood's ligament forms a suspensory hammock to support the eye and that the ligament extends to fuse with the fascia of the lateral rectus muscle on one side, and with that of the medial rectus muscle on the other. It has always been my custom, in operating on the medial and lateral rectus muscles, to cut freely Tenon's capsule along the lower margins of these two muscles. I have never been aware of any dropping of the globe, but possibly I have missed it. I should like to know what Dr Fink thinks about this.

DR HAROLD F FALLS, Ann Arbor, Mich. Dr Fink's meticulous anatomic research and carefully weighed conclusions deserve the grateful thanks of all ophthalmic surgeons. The late Dr White, of New York, was untiring in his efforts to point out that a greater effect could be obtained from tenotomy of the inferior oblique muscle at its insertion than at its origin. The anatomic explanation of this observation has, conceivably, been furnished by Dr Fink in his demonstration of the frequent firm union between the fascial sheaths of the inferior rectus and the inferior oblique muscle. Such fusion of the fascial sheaths could well serve as a new site of origin for the inferior oblique muscle after myectomy or tenotomy at its origin, and may thus account for frequent poor, inadequate results. It is unfortunate that there are not available adequate or specific clinical signs which would permit one to judge before operation whether or not a firm union is present. With respect to surgical intervention on the inferior oblique muscle, I feel strongly that a recession of the muscle at its insertion is to be preferred to a myectomy or a tenotomy performed at either the origin or the insertion. There is no more excuse today for performing a tenotomy of the inferior oblique muscle than one of the inferior rectus. Experience has taught that a carefully placed recession is to be preferred, for if it is necessary to correct or to increase the result, little difficulty is encountered in again locating the muscle. If, however, the surgeon prefers tenotomy, I urge that it be done at the insertion, for, again, it is technically simpler.

and can be corrected if overaction results. In my hands, myectomy at the site of origin has been a poor surgical procedure, for it is technically unsound and its effects are permanent and unalterable. Dr Fink points out that "it is important to sever all of the inferior oblique sheath, as well as the entire insertion of the muscle," and in this statement I concur.

I am pleased that Dr Fink has emphasized the importance of the check ligament of the inferior rectus muscle, especially with reference to its attachment to the tarsus of the lower lid and the conjunctiva of the lower cul-de-sac. This relation must be kept in mind by the surgeon when attacking the inferior rectus, for excessive recession of this muscle will pull down the lower lid and effect a widened palpebral fissure. It is equally true that excessive resection of the same muscle will narrow the vertical width of the palpebral fissure. Duane was aware of this and pointed out that a recession of the inferior rectus should not exceed 3 mm and that a resection should be limited to 5 mm. Dr F B Fralick, in his Academy course on ocular anatomicosurgical principles, points out that most visual activity lies well below the horizontal plane, and thus falls into the sphere of action of the inferior rectus muscle. The surgeon is cautioned to avoid any operative procedure that would cripple the action of this muscle. Dr Fink also cautions the surgeon to evaluate any surgical procedure with all the anatomic facts in mind for any ill advised procedure not only may be ineffectual but may cripple the action of more than one muscle. When conclusions based on both clinical and research experience are so similar, it certainly behooves the ophthalmic surgeon to be more careful in his choice of the operative procedure in each case.

DR WALTER H FINK, Minneapolis. In his daily contact with problems of the extraocular muscles, the ophthalmologist occasionally encounters cases in which an oblique muscle is responsible for the defect. The management of such cases has caused me concern because of my uncertainty as to the proper procedure. This is especially so in considering surgical procedures on this muscle. From observations in a series of dissections of these muscles, it is evident that effective surgical correction can be accomplished only when the operator is thoroughly familiar with the anatomy of the area. It is particularly important that he be aware of the anatomic variations of the muscles. It may be mentioned in passing that in some cases such anatomic variation may be the important factor in abnormal action of the oblique muscles. Another factor which should receive special emphasis is the surgical approach to the inferior rectus muscle. Many operators believe that operation on this muscle should be avoided whenever possible. My dissections bear out this view, for surgical manipulation of this muscle involves disruption of the fascial attachments in this region, which are important in the check action not only of the inferior rectus but also of the inferior oblique muscle.

# Clinical Notes

## USE OF COATED LENSES IN RETINOSCOPY

GEORGE S ZUGSMITH, M D

SAN PEDRO, CALIF

**R**ECENT experience in reduction of reflection on coated camera and spectacle lenses suggested the use of coated trial case lenses<sup>1</sup> in retinoscopy. The earlier work on coating of lenses, according to Graham,<sup>2</sup> was done by Dennis Taylor, in England, as early as 1892. He observed that the layer of dust or discoloration which appeared on old camera lenses did not reduce the light they transmitted but tended to increase it. It also reduced reflection. Taylor endeavored to reproduce the effect of age but was unable to get a coating with a wavelength necessary to intercept the incident light so as to counteract its effect. However, Strong, at the California Institute of Technology, and Cartwright and Turner, at the Massachusetts Institute of Technology, developed a process

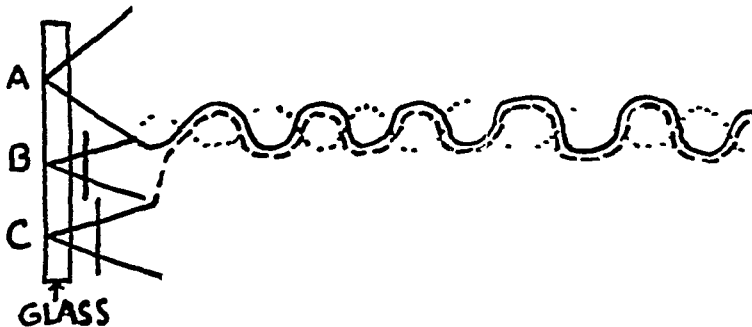


Fig 1—Alterations in wavelength of rays of light *A*, *B* and *C* produced by films of various optical thicknesses

which was used extensively in World War II on optical instruments and camera lenses. This process is the coating of the finished spectacle lens with a 0.000004 inch (0.0001 mm) thickness of a hard, inert mineral salt, usually magnesium fluoride, evaporated at high temperature and fused to the surface of the glass under a vacuum of 1/10,000,000 atmosphere. The molecular vapor thus produced condenses on the optical element to form a fairly durable and transparent layer. The coating may be applied to crown or flint glass. On crown glass there is a 6 per cent increased transmission of light, which has made the process useful for camera lenses. At the same time, intensity of light reflected by a treated lens is reduced by about 60 per cent. This is the best that can be obtained with present coatings. In order to produce zero reflection of light, the film must equal in optical thickness one fourth of a wavelength of the incident light, and the refractive index of the film must be a geometric mean of the indexes of the mediums—in this case air and crown glass. If this equation were possible, light ray *A* in the diagram (fig 1) would be

1 Suggested by Mr J Wetmore

2 Graham, R. Reduction of Reflection, Arch Ophth 36 315-320 (Sept) 1946

destructively interfered with by ray *B*, which is one-half wavelength out of phase, having passed the coating one-fourth wavelength in depth, as seen in the dotted line. If the coating were one-half wavelength thick, there would be an alteration of a full wavelength, as in light ray *C*, and thus the reflected light would be accentuated, as seen in the broken line.

It has also been shown in spectacle lenses that the coating of magnesium fluoride reduces "ghost images" due to interface reflections and gives an increase in contrast and detail. It was felt, therefore, that some of the "shadows" associated with retinoscopy might be in the class of "ghost images" and that the use of coated lenses might eliminate these to a large extent. Through the courtesy of the processing company,<sup>3</sup> a trial lens case was coated and used in this preliminary study of 100 patients. The data in the table are representative of the group.

It was hypothesized that there might be a closer relation between the retinoscopic refraction with coated lenses and the trial case acceptance

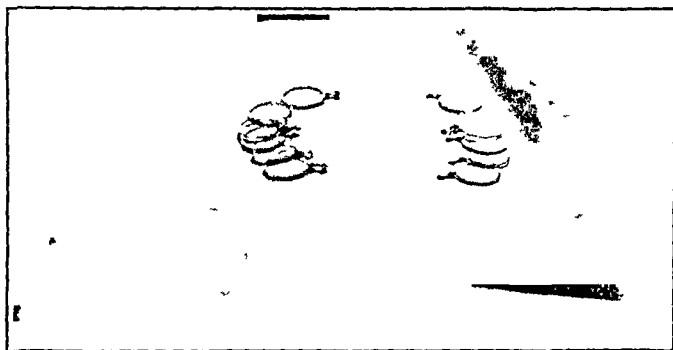


Fig 2—Coated (left) and uncoated (right) trial case lenses

This was found to be true, especially with respect to the cylindric correction and the selection of axis. Retinoscopic studies were made with coated lenses and on the same patients with uncoated lenses as a control.

However, more apparent than the statistical results was the ease with which the retinoscopic examination was performed. The shadow was much clearer and sharper with the coated lenses. The reversal point was more easily seen. There was absence of annoying side images, and in this series no scissors movement was noted in the coated lens, whereas 1 patient was seen to have such a reflex with the uncoated lenses. This aspect requires more study. There is an apparent effect of the trial frame with no lenses in it. Subjectively, the patients stated that retinoscopic examination was not as annoying through the coated lenses as through the uncoated lenses, since the brightness of the retinoscope light could be reduced. Retinoscopic examination through the undilated pupil was easier through the coated lens. In several after-

<sup>3</sup> Lane Wells Company, Lester-Lite Division, Pasadena, Calif

cataract cases the end point was seen clearly and distinctly with a minimum of distortion. The same effect was noted in several high cylindric corrections.

*Data from Retinoscopic Study of Seventeen Patients with Use of Coated and Uncoated Trial Case Lenses*

Case		Retinoscopic Refraction		Trial Case Acceptance
		Coated Lenses	Uncoated Lenses	
1	OD	-0.50 ( ) +0.25 × 90	-0.25 ( ) +0.25 × 90	-0.75 ( ) +0.25 × 90
	OS	+0.50 ( ) +0.75 × 75	+0.25 ( ) +1.25 × 90	+0.25 ( ) +0.75 × 75
2	OD	+0.25 ( ) +0.25 × 90	+0.75 × 90	+0.50
	OS	+0.25	+0.50	+0.25
3	OD	-1.00 ( ) +2.00 × 70	-1.25 ( ) +2.25 × 80	-1.00 ( ) +2.00 × 70
	OS	-1.00 ( ) +2.25 × 95	-1.25 ( ) +2.00 × 90	-1.00 ( ) +2.25 × 100
4	OD	-0.25 ( ) +1.50 × 90	-0.25 ( ) +2.00 × 75	-0.50 ( ) +1.50 × 90
	OS	+0.50 ( ) +0.50 × 75	+0.75 ( ) +0.50 × 90	+0.25 ( ) +0.50 × 75
5	OD	+0.25 ( ) +0.50 × 105	+0.25 ( ) +0.50 × 105	+0.50 × 105
	OS	+0.25 ( ) +0.25 × 75	+0.50	+0.25 ( ) +0.25 × 75
6	OD	+0.25 ( ) +1.25 × 180	+0.50 ( ) +1.25 × 180	+0.25 ( ) +1.50 × 180
	OS	+0.25 ( ) +1.50 × 165	+0.25 ( ) +1.00 × 165	+1.75 × 165
7	OD	+0.50 ( ) +0.75 × 90	+0.75 ( ) +0.75 × 90	+0.25 ( ) +0.75 × 90
	OS	+0.25 ( ) +0.75 × 90	+0.25 ( ) +0.75 × 90	+0.25 ( ) +0.75 × 90
8	OD	+1.00 ( ) +0.25 × 70	+1.25 ( ) +0.25 × 90	+1.00 ( ) +0.25 × 75
	OS	+1.25 ( ) +0.25 × 90	+1.50 ( ) +0.25 × 90	+1.00 ( ) +0.25 × 90
9	OD	+1.75	+2.00	+1.50
	OS	+2.25 ( ) +0.50 × 160	+1.50 ( ) +0.75 × 180	+2.00 ( ) +0.50 × 165
10	OD	+0.50 ( ) +0.50 × 105	+0.25 ( ) +0.75 × 90	+0.75 ( ) +0.50 × 90
	OS	+1.75 ( ) +0.25 × 90	+1.50 ( ) +0.25 × 90	+2.00
11	OD	+0.50 ( ) +0.25 × 90	+1.25 ( ) +0.25 × 90	+0.25 ( ) +0.50 × 90
	OS	+0.75 1.00	+1.00	+0.50
12	OD	+1.00 ( ) -1.00 × 90	-0.75 ( ) -1.00 × 90	-0.87 ( ) -1.25 × 90
	OS	-1.00 ( ) -1.50 × 75	-0.75 ( ) -1.50 × 75	-1.00 ( ) -1.50 × 75
13	OD	-0.25 ( ) -0.50 × 120	-0.25 ( ) +0.25 × 15	-0.50 ( ) -0.25 × 120
	OS	-1.00 ( ) +2.00 × 170	-0.75 ( ) +2.00 × 180	-1.25 ( ) +2.00 × 165
14	OD	+1.75	+1.75	+1.50 ( ) +0.25 × 180
	OS	+1.50	+1.75	+1.25 ( ) +0.25 × 165
15	OD	+1.00 ( ) -5.50 × 5	+1.25 ( ) -5.00 × 180	+0.75 ( ) -5.50 × 5
	OS	+1.25 ( ) -4.25 × 170	+1.25 ( ) -4.50 × 180	+1.50 ( ) -4.50 × 172
16	OD	+10.50 ( ) +3.00 × 30	+11.00 ( ) +3.50 × 45	+10.00 ( ) +3.00 × 30
17	OD	+9.50 ( ) +6.00 × 15	+10.50 ( ) +4.00 × 15	+9.50 ( ) +5.50 × 15

#### SUMMARY

A series of 100 patients were given retinoscopic examinations through coated and uncoated trial case lenses. There was closer correlation between trial case acceptance and retinoscopic corrections with coated lenses. The retinoscopic shadow was clearer, and side shadows were eliminated. The retinoscopic end point was easier to see. There was less complaint from the patient of discomfort due to brightness of the light.

529 West Eighth Street

# Obituaries

## ERNEST FREDERICK KRUG, M D

1877-1948

Ernest Frederick Krug died in New York on Feb 28, 1948. He was born in Cleveland, Ohio, on Oct 27, 1877, the son of Professor Joseph Krug, who for many years supervised the teaching of German in the public schools of that city. He was graduated from the College of Physicians and Surgeons of Columbia University in 1900. After finishing his general internship at the Lenox Hill Hospital, then known as the German Hospital, he went to Berlin and Vienna for the purpose of equipping himself to practice ophthalmology and otolaryngology. His strict German training and his knowledge of that language stood him in good stead throughout his professional career.

Returning to New York he completed an exceptionally thorough preparation as office assistant to Dr Emil Gruening. Over a long period he was on the staff of the New York Eye and Ear Infirmary, serving as senior assistant surgeon in the clinic of Dr Wilbur Marple. During the past twenty-five years he had devoted himself solely to ophthalmology.

In 1930 Dr Krug organized the ophthalmologic department of the Lenox Hill Hospital, which was ever near to his heart, giving to it of his time and means in fullest measure. He became associate professor of ophthalmology at the New York Post Graduate School of Medicine. He was a member of the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, and a fellow of the New York Academy of Medicine. In World War I he served with the rank of major.

Dr Krug's influence and reputation were in the main confined to those with whom he came in daily contact. He was a most excellent teacher and disciplinarian. In the course of time a succession of interns and clinical assistants had him to thank for the acquisition of a habit of paying scrupulous attention to details and for the example set by a chief who, free of envy, rejoiced more in the success of others than in his own.

His private practice was large and lucrative. Aside from remedies prescribed, his unfailing sympathy for his patients, rich and poor alike, enhanced the esteem in which the laity hold the medical profession. He has left the memory of a spotless name and of a life full of benevolences. To those of his colleagues who knew him intimately and enjoyed the hospitality of his home the sense of his loss is great and the goodness of his soul lasting.

Surviving are his wife, Louise Hoffman Krug, his sons, Ernest F Krug and Dr Joseph H Krug, who is training to follow in the footsteps of his father as an ophthalmologist, and a sister, Miss Emilie L Krug.

BERNARD SAMUELS, M D



ERNEST FREDERICK KRUG, M D  
1877-1948



## ELIAS SELINGER, M D

1898-1947

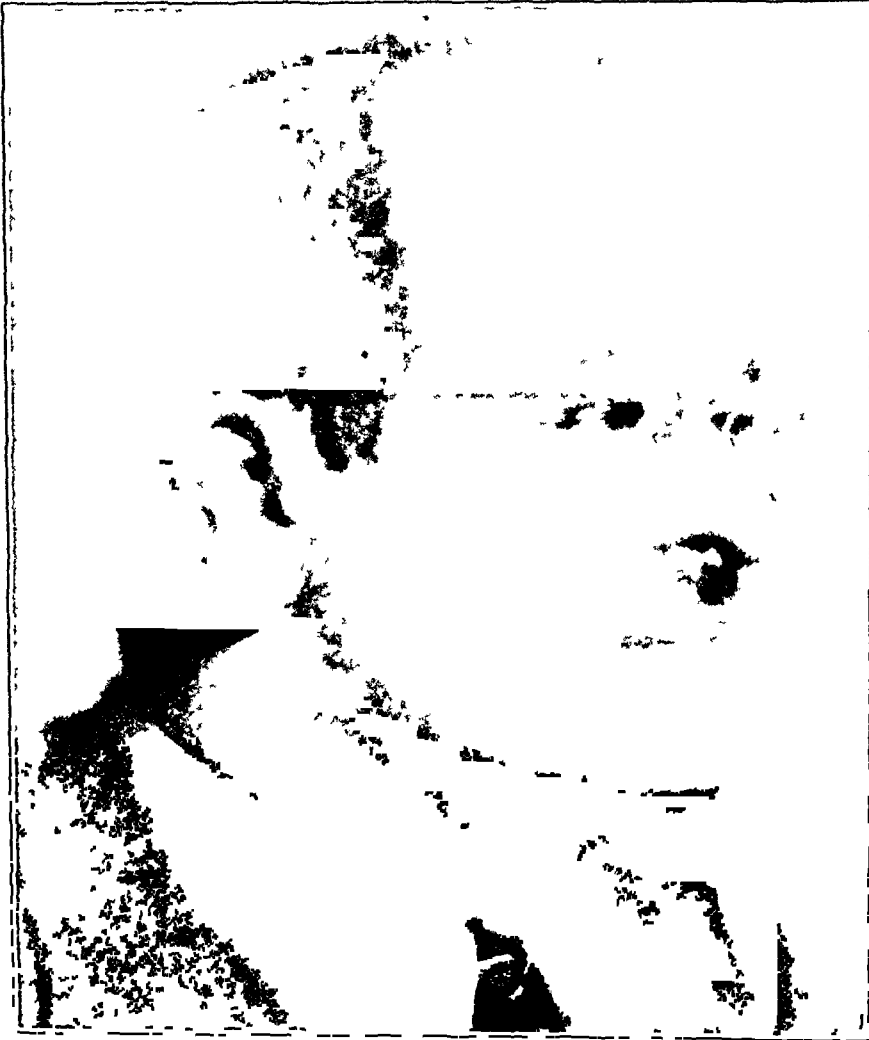
Dr Elias Selinger, while at the peak of professional activity, died at El Paso, Texas, on Dec 21, 1947, of coronary thrombosis, at the untimely age of 49. Just previous to his attack, he was busily directing the organization of the first postgraduate assembly sponsored by the Chicago Ophthalmological Society, of which he was then vice president, and was also zealously preparing for his duties as professor and chairman of the department of ophthalmology at the reorganized Chicago Medical School.

Dr Selinger was born in Moravska-Ostrava, Czechoslovakia, on Aug 23, 1898, the son of Joseph and Rosa Feuereisen Selinger. He came to this country at the age of 15 and graduated from the Northwestern University Medical School in 1924. After a general internship and a residency in the department of ophthalmology at Cook County Hospital, he continued his studies in Vienna. On his return, in 1926, he became interested in the teaching of ophthalmology, and served at Northwestern University from 1926 to 1929 and at Rush Medical College from 1929 until the dissolution of that venerable institution, in 1941, at which time he had achieved the rank of assistant professor. He received the certification of the American Board of Ophthalmology in 1931 and was a member of the American Academy of Ophthalmology and Otolaryngology, the Pan-American Association of Ophthalmology and the American Association for the Advancement of Science.

As an ophthalmic surgeon, Dr Selinger was unusually painstaking in technic and postoperative care. His numerous contributions, usually given before the Chicago Ophthalmological Society, were based on personal research or extensive clinical observation and were always admirably presented. His recent textbook on "Office Treatment of the Eye" (reviewed in the ARCHIVES 39: 118 [Jan] 1948), though prepared in the turmoil of the war years, has his characteristic clarity and thoroughness.

At the time of his death he was attending ophthalmologist to Cook County, Michael Reese and Mount Sinai Hospitals. He is survived by a wife and daughter.

JAMES E. LEBENSOHN, M D



ELIAS SELINGER, M D  
1898-1947

## Correspondence

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### GLASS IRRIGATOR TIP IN ANTERIOR CHAMBER

*To the Editor* —A case of ointment in the anterior chamber following a penetrating wound of the cornea was reported by Donald K. Binder, M D, in the December 1947 issue of the ARCHIVES, page 830. I have seen several instances of ointment globules after operation for cataract prior to the introduction of closure of the section with corneoscleral sutures. It was not deemed advisable to open the anterior chamber in order to remove a globule because the antiseptic salve always absorbed.

A more unpleasant incident is brought to mind. Low grade inflammation was noted after a cataract extraction performed on my service in a large metropolitan hospital. Biomicroscopically, a glistening reflex was observed in an exudate near the superior limbus. Examination of the glass anterior chamber irrigators revealed one with a broken tip. After the wound was opened a small piece of glass was removed which exactly matched the defect in the irrigator tip. No complications followed.

When the incident described can occur in a modern and well organized operating room, I feel justified in condemning the use of irrigators with glass tips. The Bracken metal irrigator is safer and more effective. It can also serve as a substitute for an iris spatula.

JAMES W. SMITH, M D, New York

### APPEAL FOR DONATIONS OF SLIT LAMPS AND OTHER INSTRUMENTS FOR CHINA

*To the Editor* —For the past several years a nationwide campaign has been carried on in China to combat trachoma. This is largely supported by the National Blind Welfare Association, whose sister organization in the United States is the Institute for Chinese Blind, 156 Fifth Avenue, New York. The former secretary of the campaign organization, Dr. Pang Hsien Chen, writes that the need for instruments and supplies is most urgent. Six centers and twenty-one full time and part time clinics have been set up in Free China, but such equipment as slit lamps, ophthalmoscopes, operative instruments, tonometers, microscopes, etc., are lacking. Accordingly the Howe Library of Ophthalmology is acting as a clearing house for the sending of available material to China. It is hoped that those ophthalmologists and others who have used slit lamps or other ophthalmologic equipment which they care to part with for this purpose will contact us and arrangements will be made, so long as funds for transportation become available, to send them to China. All communications should be addressed to Miss Jeanette Loessl, Howe Library of Ophthalmology, 243 Charles Street, Boston, Mass.

DAVID G. COGAN, M D, Boston

## News and Notes

EDITED BY DR. W L BENEDICT

### SOCIETY NEWS

**Deutsche Ophthalmologische Gesellschaft Heidelberg**—This society held its fifty-fourth annual meeting in Heidelberg on Aug 2 to 3, 1948. Prof Dr Engelking is secretary.

**Ophthalmologic Society of the United Kingdom**.—The annual congress of the Ophthalmological Society of the United Kingdom was held on April 8, 9 and 10, 1948, with A J Ballantyne, M D, LL D, president, presiding. The program consisted in a discussion of "Subjective Disorders of Vision" (excluding those due to local ocular diseases), which was opened by Prof H Cohen, Dr Denis Williams and Mr J H Doggat. The Bowman Lecture for 1948 was delivered by Prof Marc Amsler, of Zurich, Switzerland, on "New Clinical Aspects of the Vegetative Eye."

The following papers were presented: "Ocular Palsies Due to Infection of the Nasal Sinuses," Dr Helen Dimsdale and Mr D G Phillips, "Preliminary Survey of Forty-Five Consecutive Cases of Congestive Glaucoma," Mr J P F Lloyd, "The Conjunctival Nevus and the Neurogenic Theory of Melanoma," Mr Eugene Wolff, "The Venous Pressure in Glaucomatous Eyes," Dr T L Thomassen, "Observations on Clinical Perimetry," Dr G I Scott, "Two Cases of Special Interest" (a) "A Subconjunctival Rupture of the Globe with Extensive Migration of Uveal Pigment," and (b) "An Aneurysmal Varix of the Retina," Mr G T W Cashell, "Papilledema Associated with Toxic Hydrocephalus," Mr A G Cross, "Latent Nystagmus," Mr T Keith Lyle, "Classification of the Unassociated Dystrophies of the Fundus," Prof Arnold Sorby, "Prognosis in Detachment of the Retina," Mr C Dee Shapland, "Mode of Development of the Vascular System of the Retina, with Observations on Its Significance for Certain Retinal Diseases," Dr I C Michaelson, "Atropine in the Treatment of Glaucomatous Iridocyclitis," Prof W H Melanowski. A film "Auto-Eversion of Upper Lid (left), Voluntary Unaided," was shown by Dr W C Souter, and two pictorial demonstrations were made: (a) Spasm of the Central Artery of Retina, (b) Entoptic View of Retinal Vascularization, (c) Hypophysial Tumor Causing Homonymous Hemianopsia, (d) Hypophysial Tumor Causing Paralysis of the Third Nerve, and (e) Depigmentation of Iris in Chronic Glaucoma," Dr H M Traquair; (a) Pressure Grafting in the Contracted Socket, (b) Epibulbar Dermoid Before and After Operation, and (c) Gummatous Ulceration of the Eyelids," Dr J Ellison.

**Chengtu Eye, Ear, Nose and Throat Society**—The Chengtu Eye, Ear, Nose and Throat Society celebrated its tenth anniversary on Dec 20, 1947. Dr T H Lan, professor of biochemistry, West China Union University, the invited guest speaker, spoke on the biochemistry of blood in patients with malignant tumors. Dr K C Lang and Dr E Chan

reviewed the history and progress of the society during the past decade. A photograph was taken to commemorate the eventful occasion, and a dinner concluded the session.

**International Congress of Ophthalmology**—At a recent meeting of the International Council of Ophthalmology, held on April 7, 1948, in London, it was decided that the International Congress will meet in London in the third week of July 1950.

The following themes were chosen for the discussion: "Role of the Sympathetic Nervous System in Genesis of Vascular Hypertension and Its Effect on the Eye", "Clinical and Social Aspects of Heredity in Ophthalmology". Madame Schiff-Wertheimer, Mr Hedley Atkins and Prof Wagner will open the discussion on the first theme, Dr Schneyder, Miss Ida Mann and Professor Franceschetti, on the second.

The official languages will be English, French and Spanish.

The organizing committee consisted of Sir Stewart Duke-Elder, president, Mr Frank W Law, secretary, and Mr E F King, Mr T Keith Lyle and Mr A Seymour Philips.

**Centenary Congress of Section of Ophthalmology of Hungarian Medical Trade Union.**—The Section of Ophthalmology of the Hungarian Medical Trade Union will celebrate its centenary congress in September 1948, at Budapest. The leading topics will be (1) Chemotherapeutics, Antibiotics in Ophthalmology, and (2) Modern Ophthalmic Instruments, Surgical and Optical. The president is Prof Dr Gusztav Horay, and the secretary, Dr István Grosz, Nador utca 32, Budapest V.

**Ophthalmological Society of Australia**—The Ophthalmological Society of Australia, which is a branch of the British Medical Association, invited members of the Section on Ophthalmology of the Scientific Assembly of the American Medical Association to be represented at the annual meeting at Perth, Western Australia, Aug 15 to 21, 1948.

Dr Trygve Gunderson is secretary of the Section.

**Association for Research in Ophthalmology**—The next meeting of the Association for Research in Ophthalmology will be held in Thorne Hall, Northwestern University Medical School campus, Chicago, June 21 and 22.

#### GENERAL NEWS

**Home Study Courses Sponsored by American Academy of Ophthalmology and Otolaryngology**—The home study courses sponsored by the American Academy of Ophthalmology and Otolaryngology, in the basic sciences related to these two specialties, will be given again, beginning Sept 1, 1948. Registrations must be completed before August 15. Detailed information may be secured from Dr William L. Benedict, executive secretary, 100 First Avenue Building, Rochester, Minn.

**Albrecht von Graefe's Archiv fur Ophthalmologie**—This journal has resumed publication under the editorship of E Engelking, W Lohlein, O Marchesani and K Wessely. It is to be published by Springer-Verlag, Heidelberg and Berlin, and J F Bergmann, Munich.

**The Albert D. Frost Memorial Library.**—The Department of ophthalmology of the Ohio State University College of Medicine, Columbus, Ohio, announces the opening of the Albert D Frost Memorial Library, following Mrs Frost's gift of her husband's ophthalmologic library. Plans for a study room in connection with the library in the new medical center are being made. To maintain the library an endowment fund is needed, and an appeal is made to Dr Frost's friends and others who might be interested in this worthy undertaking. Contributions of \$5 to \$25 are solicited, checks are to be made out to the Frost Memorial Library and sent to Arthur M Cullen, M D, University Hospital, the Ohio State University.

**Delta Gamma Fraternity Fund**—The Delta Gamma Fraternity has a \$1,000 annual fund from which smaller scholarship awards are available for preparation of persons intending to become (1) orthoptic technicians, (2) teachers of partially seeing children or (3) specialists for blind preschool children. Any one wishing to specialize in one of these fields may be eligible for assistance, the amount in each case to be determined by the particular need and costs involved. Candidates for training in one of these fields should apply for a scholarship to Mrs Richard P Miller, 39 West Jefferson Road, Pittsford, N Y.

Candidates are selected with the advice of a professional committee chairman, LeGrand H Hardy, M D, of the American Orthoptic Council, Mrs Virginia Smith Boyce, administrative assistant, National Society for the Prevention of Blindness, Inc, Miss Ruth E Lewis, professor of social work, George Warren Brown School of Social Work, Washington University, Dr Berthold Lowenfeld, director of educational research, American Foundation for the Blind, Miss Ruth B McCoy, assistant director, New York State Commission for the Blind, and Lillian Ray Titcomb, M D, president of executive committee, Nursery School for Visually Handicapped, Los Angeles.

**Annual Examination for Orthoptic Technicians**—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in September and October 1948.

The written examination will be nonassembled and will take place on Thursday, September 9, in certain assigned cities and offices and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, October 9, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the secretary of the American Orthoptic Council, Dr Frank D Costenbader, 1605 Twenty-Second Street, N W, Washington 8, D C, and must be accompanied with the examination fee of \$25.

**Scholarships Established by the Lions Club of New York**—The Lions Club of New York has presented a check for \$2,000 to the New York University College of Medicine to finance four scholarships for graduate training in ophthalmology

The scholarships were awarded to Dr Goodwin M Breinin and Dr Walter J Maher, of New York, Dr Edwin H Kent, of Riverside, Conn, and Dr Charles H Toomey, of Lakewood, Ohio They will study special phases of eye conservation at Bellevue Hospital under the direction of Dr Daniel B Kirby, chairman of the Department of Ophthalmology at the College of Medicine

**Argentine Congress of Ophthalmology.**—The meeting of the Argentine Congress of Ophthalmology will be held in Mar del Plata from Dec 13 to 18, 1948 The main subject will be "Tumors of the Visual Apparatus"

**Medical Journals Needed Abroad**—Requests from libraries, medical societies and individual physicians in various devastated countries are being received almost daily If physicians have extra copies of medical journals or copies for which they have no further use, it will be greatly appreciated if they will send them to the headquarters of the Association for distribution abroad

# Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

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## Cornea and Sclera

ALLERGY TO ENDOGENOUS HORMONES AS A CAUSE OF KERATITIS  
ROSACEA B ZONDEK, J LANDAU and Y M BROMBERG, Brit J  
OPHTH 31:145 (March) 1947

The authors supply the following summary

Six patients (3 men and 3 women) with keratitis rosacea associated with rosacea faciei of long duration which had proved refractory to the usual methods of treatment were examined for hypersensitivity reactions to endogenous hormones. In all cases allergy to testosterone was demonstrated by positive cutaneous reactions to intracutaneous injection of the substance. Other hormones (estione, estradiol [dihydrotheelin], progesterone, pregnandiol, corticosterone, insulin and gonadotropin) gave negative reactions. Desensitization treatment by a course of subcutaneous injections of testosterone in gradually increased doses and implantation of pellets containing 10 mg of testosterone propionate produced satisfying results. Testosterone gave relief only when given in low, gradually increased doses, administration of large doses may cause a severe exacerbation. The finding of an allergic reaction to endogenous testosterone in a small number of cases of keratitis rosacea does not exclude the other possibilities

W ZENTMAYER

## Glaucoma

CYCLODIALYSIS A FOLLOW-UP STUDY H S SUGAR, Am J Ophth  
30:843 (July) 1947

Sugar found that a relatively small number of successful cyclo-dialyses, after varying periods, became failures or relative failures. In Chicago, the recent trend has been away from cyclodialysis and toward iridencleisis. Cyclodialysis is more successful if the ciliary body is separated from the scleral spur along a third of the circumference of the angle, preferably by use of the Blaskovics technic

W S REESE

INVERSE CYCLODIALYSIS R N SHAFFER, Am J Ophth 30:860  
(July) 1947

Shaffer believes that so-called inverse cyclodialysis is safer and more successful, particularly if combined with injection of air. Gonioscopic control of the site of operation is essential. He reports 2 cases and gives statistics for 21 cases

W S REESE

THE RELATIVE VALUE OF SEVERAL DIAGNOSTIC TESTS FOR CHRONIC  
SIMPLE GLAUCOMA S BLOOMFIELD and L KELLERMAN, Am J  
Ophth 30:869 (July) 1947

Bloomfield and Kellerman found the lability test the most dependable, the most convenient and the quickest of the diagnostic tests



for glaucoma The water-drinking test followed closely in reliability In decreasing order of dependability were the dark room test, the caffeine test and the response to mydriasis induced with paredrine hydrobromide ophthalmic (a 10 per cent solution of *p*-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved with merthiolate, 1:50,000)

W S REESE

## Injuries

INTRAOCULAR FOREIGN BODIES IN SOLDIERS H C WILDER, *Am J Ophth* 31:57 (Jan) 1948

Wilder briefly discusses intraocular foreign bodies in soldiers from a study of 731 enucleated eyes at the Army Institute of Pathology In 37 per cent they were magnetic, in 62 per cent nonmagnetic and in 1 per cent mixed There were 5 eyes with sympathetic uveitis

This study confirms previous observations that in military injuries nonmagnetic foreign bodies predominate, but many instances of successful extractions do not come to the pathologist's attention, and even in eyes that are enucleated nonmagnetic foreign bodies are often secondary to ferrous missiles, which have been extracted The infections and reactions associated with the different types of foreign bodies ranged from staphylococcic infection, resulting in purulent panophthalmitis, to the mild inflammatory reaction associated with siderosis bulbi and intraocular hemorrhage without infection Giant cells were particularly abundant around vegetable matter and eyelashes Of particular interest were 5 cases of sympathetic uveitis, associated with retained nonmagnetic material in 4 cases and with a retained ferrous foreign body in 1 Phthisis bulbi was a common end result, and glaucoma was comparatively rare, as in any series of penetrating wounds

W ZENTMAYER

INTRAOCULAR FOREIGN BODIES AN ACCOUNT OF MILITARY CASES FROM THE BURMA-ASSAM FRONT E J SOMERSET and K SEN, *Brit J Ophth* 32:13 (Jan) 1948

Operation was performed only in those cases in which two criteria were fulfilled those in which there was a retained intraocular foreign body and those in which there was at least light perception with fair projection A selected series of 29 cases are described In 13 cases the foreign body could be seen with the ophthalmoscope In 16 cases the ring method of localization was employed Of the 6 anterior route operations, 5 were successful and 1 failed In 23 cases the posterior route was used In 17 cases, the foreign body was removed, and in 6 it failed to come out The percentage of extractions was 75.8 With multiple foreign bodies, unless all came out, the operative result was recorded as a failure

The author gives the following summary A description of 29 cases of intraocular foreign bodies, mostly from Japanese grenades in the Assam-Burma Front is given The low magnetic properties of the frag-

ments necessitated posterior route extraction in most cases. Ring localization proved accurate, and the Haab test was of little value, and was often misleading. The main causes of visual defect were vitreous hemorrhage and cataract.

W. ZENTMAYER

### Lacrimal Apparatus

LIPIODOL [IODIZED OIL U. S. P.] STUDIES OF CHRONIC DACRYOCYSTITIS. S. A. Fox, *Am J Ophth* 30:878 (July) 1947

Fox found that roentgenologic studies tended to confirm the belief that chronic dacryocystitis is an ascending infection from the nose or the paranasal sinuses, and that the dilatation of the sac is always forward and greater below the internal canthal ligament.

W. S. REESE

### Orbit, Eyeball and Accessory Sinuses

CONTRACTED SOCKET. THE SPLINT METHOD OF POST-OPERATIVE CONTROL. F. M. LYONS, *Brit J Ophth* 31:703 (Nov) 1947

Briefly, the epidermal graft is applied to the prepared socket in the usual way, but on a special acrylic mold. At the first dressing (i. e., on the seventh day) the mold is connected to a rigid, but adjustable, splint. The fixed point is a frontal pin embedded in a plaster of paris head cap, and to this the mold is attached with stainless steel rods and universal clamps.

W. ZENTMAYER

A PLEA FOR LATERAL ORBITOTOMY (KRONLEIN'S OPERATION). H. B. STALLARD, *Brit M J* 1:408 (March 29) 1947

Dandy, in 1943, stated that in 70 to 80 per cent of the cases of orbital neoplasm which cause unilateral proptosis both the orbit and the cranial cavity are involved, and he advocated the transfrontal route, as it is rarely possible before operation to be certain whether or not the tumor lies also within the cranial cavity. Harvey Jackson (*Proc Roy Soc Med* 38:587, 1945) stated "that by careful clinical examination, by judicious radiography and by suitable application of laboratory investigation, not only is the diagnosis of tumor to be reached but its ramifications regularly revealed and not infrequently its pathological nature surmised." Jackson concurred in Dandy's opinion that the transfrontal route is preferable in every way, as a more adequate exposure is obtainable and any extension intracranially can be approached. With this operation, there is less interference with ocular motility and there remains no visible and ugly scar, and it is not true that pulsating of the eye remains.

Stallard expresses the belief that lateral orbitotomy affords a more direct and more adequate exposure in cases of tumor limited to the orbit, and that good stereoscopic roentgenograms of the orbital walls and the optic foramina and canals are helpful in excluding extraorbital extension. There is no reason to fear an ugly scar.

He then describes a case of unilateral proptosis, due to a neurofibroma 30 by 23 by 16 mm situated within the muscle cone and beneath the optic nerve. Transfrontal craniotomy failed to reveal the neoplasm, and six months later, after a temporary removal of the lateral portion of the orbit, the tumor was successfully removed. Vision recovered from perception of hand movements only to 6/6, and the field of vision improved by 35 degrees.

ARNOLD KNAPP

### Retina and Optic Nerve

A CASE OF PSEUDO-GLAUCOMA J A MAGNUS, Brit J Ophth 31 692 (Nov) 1947

A man aged 74 had vision of 6/9 + in the right eye and 6/9 part in the left eye. The right field showed a marked nasal step reaching fixation and a typical arcuate scotoma, the left field showed general peripheral depression. The field for red was disproportionately depressed. The intraocular tension was 19 mm mercury and did not rise after instillation of homatropine. There was deep cupping of the optic disks. Roentgenogram showed calcification of the internal carotid artery.

W ZENTMAYER

SOLAR RETINITIS E ROSEN, Brit J Ophth 32:23 (Jan) 1948

Rosen states that in the past year he has seen a great many cases, during routine examination, of small, easily overlooked macular holes. In all cases a history was elicited of "sun gazing" or a related act. The clinical history of 23 cases is tabulated, and fundus drawings of 21 cases are supplied.

The author has observed over 500 cases of small macular holes in "colored" troops, in none of which the patient was vasoneurotic and in every one of which there was a history of exposure to the direct action of the sun's rays.

W ZENTMAYER

ORIENTATIONS IN THE TREATMENT OF RETINAL THROMBOSIS  
M ESTEBAN, Arch Soc oftal hispano-am 4:106 (Jan-Feb) 1944

This condition, which according to Schobl occurs in 1 of 180,000 patients, and according to Dufour in 1 of every 5,000 patients, is usually considered from the ophthalmoscopic standpoint. Little, if anything, has been said about its treatment.

Three factors are concerned in its causation: alterations in the vascular endothelium, a blood status favoring rapid coagulation and slowing of the venous circulation. Treatment is directed to these factors by eliminating distant foci of infection, treating systemic infections with serum, vaccines and sulfonamide drugs; diminishing the clotting properties of the blood by use of sodium citrate, hirudin or heparin, and improving the local circulation by the use of derivatives, leeches and massage. A case is presented in which the treatment was used.

H F CARRASQUILLO

### Trachoma

PENICILLIN TREATMENT OF TRACHOMA D J DARIUS, *Am J Ophth*  
28: 1007 (Sept) 1945

Darius reports encouraging results in a series of 12 cases of trachoma treated with topical application of the sodium salt of penicillin in a solution of 500 units to each cubic centimeter of water. He reports 2 illustrative cases.

W S REESE

TREATMENT OF TRACHOMA WITH ALBUCID [SULFACETIMIDE] H  
VALENCIA, *Arch Soc de oftal hispano-am* 3: 432 (Nov-Dec)  
1943

The author's experience is in agreement with that of other observers as to the prompt disappearance of subjective symptoms and the rapid improvement of the corneal lesions of trachoma after the use of sulfacetimide, but he disagrees with authors who state that there is no action on the granulations and that the conjunctival swelling is diminished only at the beginning. Valencia has seen cases in which the granulations disappeared entirely in four days when sulfacetimide was used in large doses.

He draws the following conclusions: Sulfacetimide is efficacious in relieving the subjective symptoms and the corneal lesions of trachoma; it also acts on the specific conjunctival lesions when used locally; it is adjuvant in treatment, and the preparation is perfectly tolerated by the great majority of patients.

H F CARRASQUILLO

### Tumors

TUMORS OF THE EYE IN TURKEY NURI FEHMI AYBERK, *J A M A*  
135: 373 (Oct 11) 1947

Before the Turkish Medical Society of Istanbul, Dr Nuri Fehmi Ayberk reported his experience as ophthalmologist to the Haidar Pasha Model Hospital. He discussed at length 27 tumors of the eye encountered among the 70,000 ophthalmic patients he examined during the last ten years. There were 13 epitheliomas of the eyelids, 8 in men and 5 in women, between the ages of 40 and 70. Of the 27 tumors, 60 per cent were located at the inner angle of the eyelid. Dr Ayberk attributed this location to age and occupation, advanced age causing relaxation of the orbicularis muscle and eversion of the lacrimal point, and the occupation of farming engaged in by the majority of these patients leading to chronic conjunctivitis, due to exposure of the eyes to strong sunlight and dust. These causes give rise to continuous lacrimation, causing irritation of the skin and obliging the patient to wipe the affected region often, thus facilitating the development of the tumor. Of the tumors of the conjunctiva, 1 was a papilloma arising on the upper eyelid, the other, resembling a melanosarcoma, proved to be a benign tumor originating at the lacrimal caruncle. Dr Ayberk saw 7 carcinomas of the eyeball. There were 3 internal tumors of the eye, 1 primary sarcoma of the choroid and 2 gliomas. Of the tumors of the orbit, 1 was an osteoma and 1 a benign tumor of the optic nerve. In conclusion, Dr Ayberk said he had not seen any tumors caused by parasites.

W ZENTMAYER

A CASE OF AN ADENOMA ARISING IN A SWEAT GLAND OF THE UPPER LID F CLIFTON and W H GORDON, Brit J Ophth 31:697 (Nov) 1947

There was present a rather flattened, oval tumor with the long axis vertical and the lower pole overhanging the lid margin. The growth was encapsulated. The structure of the tumor resembled a tubuloracemose gland. In places there was proliferation of the parenchymal cells as solid masses, between some of whose cells cell bridges could be made out. Many degenerative cysts, in all stages of development, were seen in the cell masses.

W ZENTMAYER

Uvea

DETACHMENT OF THE CHOROID AND THE RETINA G H STINE, Am J Ophth 30:897 (July) 1947

Stine, as an aid to correct diagnosis, describes the sign of ophthalmoscopic retroillumination or paraillumination, which is diminished or absent in cases of choroidal detachment and exaggerated in cases of serous retinal separation. He discusses anatomic and topographic relations of the vorticos veins and describes a method of orthographic projection to show precisely their action in localizing and limiting the size of choroidal detachments.

W S REESE

Therapeutics

THE APPLICATION OF PENICILLIN IN OPHTHALMOLOGY D BEREZINSKAYA, Vestnik oftal 24:13, 1946

Berezinskaya employed both Soviet and American-made penicillin. The Russian penicillin evidently has more bacteriostatic effect than the American penicillin, as the quantity required was much less than that of the American. In 1944 penicillin from *Penicillium crustosum* (Russian) was used in 20 cases in a military hospital, in a dose of 500 or 600 units three to four times a day. No local or general reaction was observed. In 1945 American penicillin was used in 14 cases, the dose being about 90,000 to 100,000 units a day. Penicillin gave excellent results in 13 cases with blepharitis and corneal ulcers. Of 11 cases of uveitis, penicillin therapy was effective in 4, of these, 2 were of tuberculous and 1 of rheumatic origin, and in 1 the cause was unknown. In the others the subjective symptoms were improved. In 1 case of sympathetic ophthalmia penicillin produced notable improvement in both eyes (the eye operated on for cataract, the exciting eye, was not removed, as vision in this eye was better than in the other) after two days of intramuscular injections. The treatment had to be repeated three times, after which vision was improved to 0.4 in one eye and to 0.8 in the other eye. In treatment of purulent infections of the lids and orbit local applications and intramuscular injections should be combined. In order to avoid the development of resistance to penicillin, the drug should be given intensively in the first stage of the infection.

O SITCHEVSKA

# Society Transactions

EDITED BY DR W L BENEDICT

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COLLEGE OF PHYSICIANS, PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Burton Chance, M D , *Chairman*

George F J Kelly, M D , *Clerk*

*March 20, 1947*

## Factors Operative in Absorption from the Vitreous. DR LUDWIG VON SALLMANN, New York

In view of the difficulties in examining the exchange of fluids in the posterior segment of the eye by the orthodox method, a new approach was selected with the practical aspect of the problem in mind. The experiments were grouped (1) according to phenomena of diffusion in the vitreous and of its liquefaction, (2) in relation to the activity of the ciliary epithelium, (3) according to the influence of the basal metabolism, and (4) on the basis of clinical methods used to speed up absorption from the vitreous.

The dependence of the diffusion of hemoglobin on the structural integrity and the viscosity of the vitreous was studied by injecting pig's hemoglobin into fresh intact pig's vitreous. When the latter was exposed to a temperature of 37.5 C, the hemoglobin diffused throughout the vitreous within eighteen hours, whereas the spread was slow at refrigerator temperature. When hemoglobin was injected after autolysis of the vitreous had taken place on storage of the preparations for twenty-four hours at room temperatures, no difference in the diffusion of the hemoglobin was noticed at various temperatures. It was concluded that autolytic liquefaction, or lowering of the viscosity of the vitreous, had resulted in rapid diffusion in the eyes which had been exposed to 37.5 C in the first series of experiments.

The effect of liquefaction on diffusion or spread and absorption of foreign matter was investigated in an extensive series of *in vivo* experiments on 24 rabbits. Partial liquefaction was induced by injecting various amounts of a purified and concentrated preparation of hyaluronidase made by Dr Karl Meyer from bull testes, this mucolytic enzyme acts on the substrate of the vitreous. The enzyme dilutions were introduced together with suspensions of the animal's own red cells, which served as the test substance. Early spread of the red cells and moderately accelerated absorption were observed clinically and histologically in the eyes which had received more than 10 micrograms of the enzyme. When the dose exceeded 50 micrograms, the treatment elicited a conspicuous inflammatory response from the inner membranes of the eye. Even 2 of 5 eyes of the series receiving 50 micrograms reacted with pronounced signs of inflammation. The rest of that group and the eyes given injections of 10 or 25 micrograms exhibited early loosening of the clot of red cells and somewhat earlier absorption, without apparent toxic side action. It seemed that the partial liquefaction induced by the mucolytic enzyme caused the early spread of the red cells in the

vitreous, and this, in turn, may have facilitated the more rapid breakdown of the erythrocytes and their absorption. It is evident that at present the toxic action of a medium dose of the enzyme obviates its practical use.

The problem of active absorption possibly exercised by the ciliary epithelium was studied on the basis of R. Hoeber's work on the active transfer of a group of sulfonic dyestuffs through the wall of the proximal tubules of frog kidneys. Hoeber found that this transfer depended on the polar-nonpolar configuration of the dyestuffs, since the dyes with the sulfonic groups attached to one of the benzene or naphthalene rings were transferred through the wall, in contrast to the dyes in which each of the benzene or naphthalene rings carried a sulfonic radical. The present experiment on albino rabbits, albino rats and frogs with the use of various technics did not give evidence that the dye in the vitreous had penetrated the ciliary cells or had accumulated in intracellular vacuoles except in 1 of 60 eyes. Despite the negative results, further studies are warranted.

The influence of the basal metabolism on resorption was again studied on suspensions of the animal's own red cells injected intravitreally. Five litters of albino rats (34 animals) were divided into three groups so that litter mates were distributed among the three series. The first group, of 12 rats, were thyroidectomized by Dr. G. Smelser when the rats were 2 weeks old. The second group, of 12 animals, received daily subcutaneous injections of thyroxin, 1 mg per hundred grams of body weight. After the injection of a small amount of the animal's own red cells, the density and extent of the cellular deposits in the vitreous were estimated by ophthalmoscopic examination and graded. The 68 eyes were examined three times a week, and the graded findings were tabulated so that the resorption could be expressed in curves when plotted against time. Thyroxin had no clear effect on the growth of the animals or on resorption of red cells from the vitreous, as compared with the results for a control series of 10 untreated normal animals. The thyroidectomized rats showed greatly retarded growth and, in general, flat resorption curves, that is, the red cells disappeared more slowly from the vitreous than in the 20 control eyes.

The last group of experiments was designed along the line of clinical methods used in the therapy of hemorrhages and other opacities of the vitreous. The effects of subcutaneous and subconjunctival injections of hypertonic solutions of sodium chloride, of iontophoresis and of artificial fever were examined. The animal's own red cells or a concentrated solution of insulin introduced into the vitreous was the test substance. Only the short bouts of fever induced daily for two weeks had in rats an indisputably beneficial effect on the rate of disappearance of the red cells from the vitreous (40 animals).

#### DISCUSSION

DR IRVING H. LEOPOLD. The vitreous humor has been the subject of investigation by numerous men for many years and has involved a knowledge of special technics, of physical chemistry and of ophthalmology. Men such as Duke-Elder, Robertson, Hodgeson, Goedble and Haurmann have worked on this problem for years. No one has contributed more to present knowledge of the vitreous than has Dr

von Sallmann It was a pleasure to hear him discourse on aspects of the vitreous, for on this subject he is certainly an authority

The vitreous humor is a colloidal structure, and as a colloidal structure may exist as a sol or a gel. Sols are colloidal states in which the solid particles are dispersed in a fluid medium, and gels are colloidal states in which the solid particles, so to speak, join hands and form a framework in which the liquid medium is dispersed.

Most of the evidence—and much of the more recent evidence has been contributed by Dr. von Sallmann—indicates that the vitreous humor is a gel. It is not a very stable gel. The liquid and the solid phase are in unstable equilibrium, and this can be upset easily. When the vitreous gel is disturbed the transparency of the vitreous is altered.

There are two ways, roughly, in which the transparency of the vitreous can be changed, with the production of opacities: first, by disturbance of the gel of the vitreous; and, second, by the influx of new materials, such as red cells, exudates and foreign bodies. An example of the first mechanism is the formations of senile opacities in the vitreous. These are thought to be due to the aging of the gel, which changes into the sol state. All gels tend to break down to the sol state as they age. Myopic opacities of the vitreous are thought to result from movement of the vitreous gel in an enlarged globe. Liquefaction of the vitreous gel by proteolytic enzymes may result in opacities.

The other group of opacities is due to the influx of new material, such as red cells, which Dr. von Sallmann has discussed. The problem of intraocular hemorrhage is a serious one. The treatment of hemorrhage in the interior chamber is still unsolved, but hemorrhage in the vitreous offers an even greater therapeutic problem. Treatment of hemorrhage in the vitreous is concerned not only with resorption of blood but with maintenance of the *status quo* of the vitreous gel, or its reconstruction if it is disturbed. Dr. von Sallmann has given us some ideas concerning the method of resorption of the cells, but, at the same time, he has suggested methods which disturb the structure of the vitreous body.

It is interesting to observe workers in other fields of medical science turning to the eye as an aid in solving their own problems. This has happened in the case of the diffusion factor. Dr. von Sallmann has reviewed their observations and has added his own in order to solve some ophthalmologic problems. Duran Reynals found that if vaccinia virus was injected into the testes of rabbits one could be more certain of "takes" than if the injections were made in other areas of the body. He could get a much severer infection with such injections. He then found that if an extract of the testes was injected into the skin prior to injections of vaccinia he could also facilitate systemic spread of the virus and increase the number of "takes." He thought that the testis extract facilitated the spread of the vaccinia by hydrolyzing the viscous mucoproteins in the connective tissues.

These diffusion factors were then found to hydrolyze hyaluronic acid. Karl Meyer and his co-workers isolated this mucopolysaccharide from the vitreous humor. Other investigators then turned to the vitreous, an excellent substrate of hyaluronic acid, as a place in which to compare and study the activity of various diffusion factors. They measured the ability of the various diffusion factors to reduce the viscosity of the



vitreous humor Most such factors are thought to act through hydrolysis of hyaluronic acid However, ascorbic acid is also known to reduce the viscosity of the vitreous It does not work theoretically, as do the other diffusion factors, for that reason, many people do not consider it a factor in spread Nevertheless, it can, when properly employed, reduce the viscosity of the vitreous humor, and it is quite possible that it may help in this manner in the resorption of hemorrhage in the vitreous Vitamin C has been used in the past as therapy in intraocular hemorrhage It was thought that it built up intercellular cement substance and reduced the capillary permeability, thus preventing further bleeding It was not generally realized that it might reduce the viscosity of the vitreous and facilitate greater distribution of red cells and earlier resorption It may not be as toxic as hyaluronidase and perhaps can be injected directly into the vitreous without producing the untoward effects of this substance

The observations of the influence of thyroidectomy on resorption of blood are worthy of note In 1936 Jeandelize and Drouet reported on cases of recurring hemorrhage in the vitreous They reported that all their patients with this disorder had some degree of hyperthyroidism and expressed the belief that they could prevent recurrences by irradiating the pituitary body, thus producing lowered activity of the thyroid gland It is interesting that the lower activity of the thyroid may work toward the prevention of hemorrhagic recurrences and, at the same time, retard the resorption of existing hemorrhages

For years men have recommended fever therapy or shock therapy for resorption of hemorrhage in the vitreous, most of them without any well founded controlled experiments on which to base their choice of therapy Dr von Sallmann has given us controlled data to show the value of artificial fever

There is some question about the circulation of fluid in the vitreous humor As you know, the vitreous body is not thought to have any metabolism It is supposed to be a product of the surrounding cells It probably does not utilize oxygen or produce carbon dioxide Regardless of this lack of necessity for metabolic interchange, there is some evidence of a flow of fluid through the vitreous This has been demonstrated in rabbits, but not satisfactorily in man The flow is thought to be from the ciliary body toward the optic nerve Certainly, the diffusion of the red cells would not tend to substantiate the idea of such a direction of flow in the vitreous The diffusion was in all directions of flow in the vitreous

There is no doubt that papers such as Dr von Sallmann's give one considerable information with which to further knowledge of the vitreous body and, at the same time, furnish concrete evidence on which to base future therapy of the disorders of the vitreous

DR FRANCIS HEED ADLER I had not intended to discuss this paper, largely because of a feeling of inadequacy I rise, as they say in parliamentary language, to a point of order, i e., to object to the statement in Dr von Sallman's paper in which he mentioned my name as having anything to do with furthering knowledge of the vitreous Although long ago, in those halcyon days, I was interested in some of the physiologic problems of the vitreous, the work to which he refers is chiefly

a study in my laboratory carried out by Dr Irving Leopold, and the full credit should be given to him

Dr von Sallmann's paper brings up many practical problems, and it is just such careful investigations as these which open the way to new therapeutic attacks on clinical problems

From what has been said about hyaluronidase, it seems to me that the approach through its use is practically closed. The threshold of what is experimentally demonstrable in its effects lies too close to that which is also demonstrable in producing retinal damage. This situation is comparable to that of some anesthetics which perhaps are good anesthetics but for which the threshold of anesthesia is very close to that of death.

I should be interested in having Dr von Sallmann comment further on thyroxin, particularly in relation to its water-binding properties, and the role of the hormone of the anterior lobe of the pituitary gland in the production of exophthalmos. I wonder whether he has taken into consideration the relation of thyroxin to the hormone of the anterior lobe of the pituitary in this respect, and whether he has anything further to say on this subject. I think that it is a lead which offers something.

Finally I can confirm, as can all of us here, the clinical effects of fever therapy on the absorption of hemorrhage in the vitreous. That is certainly *fait accompli* and is one of the most reliable medical measures at present.

DR LUDWIG VON SALLMANN, New York. I want to thank Dr Leopold and Dr Adler for their interesting discussions. I am sorry that I cannot offer anything on the significance of the thyroxin experiments to the function of the pituitary gland. I did not go into detail concerning the injections of thyroxin because the results were erratic. Sometimes a fairly significant increase in absorption of the red cells was obtained, but in other cases there were flat absorption curves.

DR FRANCIS HEED ADLER. Why did you use thyroxin? What theoretic consideration led you to suspect that thyroxin might have some effect on the absorption of the hemorrhages in the vitreous?

DR LUDWIG VON SALLMANN, New York. Hans Eppinger, in 1914, studied the effect of thyroid preparations on the water threshold and described the rapid absorption of tissue fluid in certain types of edema. These observations on the water threshold and the stimulation of the basal metabolism by thyroxin were the theoretic basis of my experiments.

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Fifty-First Annual Meeting, Chicago, Oct 14-17, 1946

**Beta Irradiation in Ophthalmology.** DR CHARLES E. ILIFF, Baltimore

This paper, one of three read at a symposium on irradiation therapy in otolaryngology and ophthalmology, was published in a previous issue of the ARCHIVES (38:415-441 [Oct] 1947)

**Tests of Heterophoria** DR RICHARD G SCOBEE and DR EARL L GREEN, St Louis (by invitation)

The reproducibility or reliability of measurements of heterophoria when made by two examiners with the tangent screen-Maddox rod test was found in one sample of aviation cadets to be satisfactorily high. The coefficients of reliability were  $+0.95$  for lateral heterophoria and  $+0.92$  for vertical heterophoria at a testing distance of 20 feet (6 meters). In another sample, after removal of systematic effects due to the use of screening and to changing the color of the rod, the Maddox rod test both at 20 feet and at 13 inches (30 cm) had a reliability coefficient of  $+0.97$  for lateral heterophoria.

There is no significant difference in results obtained by two different examiners in administering the tangent screen-Maddox rod test.

Several tests for heterophoria were compared with the screen and parallax test which is considered the most accurate. At a testing distance of 20 feet, a high correlation was found with von Graefe's prism diplopia test and with the screen-Maddox rod test. At a testing distance of 13 inches, a high correlation was found with von Graefe's prism diplopia test, the Maddox wing test and the Thorington test. The correlation with the screen-Maddox rod test was somewhat lower in one experiment but high in another.

The effect of varying the testing conditions on the Maddox rod test was determined. The amount of illumination had no significant effect. It makes no difference whether the Maddox rod is placed over the dominant or the nondominant eye. At a testing distance of 20 feet a red Maddox rod uncovers more esophoria than does a white one but there is no difference between the effect of the red and that of the white rod at 13 inches. With screening the Maddox rod test uncovers more esophoria or less exophoria than without screening.

The Maddox rod test for all possible combinations of four alternative testing conditions was found to be highly correlated with the screen and parallax test.

The following conclusions may be drawn from the results.

(a) For heterophoria measurements may be performed with sufficient accuracy to discriminate between subjects.

(b) The Maddox rod test gives results sufficiently like those of the screen and parallax test to be used as a replacement for it for purposes of routine testing.

(c) It is recommended that the Maddox rod test be performed with a white rod, without screening and without regard to placing the rod before the dominant or the nondominant eye for purposes of routine testing.

#### DISCUSSION

DR JOHN H DUNNINGTON, New York. The findings in this careful statistical survey of tests for heterophoria furnish much food for thought. The scrupulous care with which the tests were done makes their results all the more valuable. The authors have demonstrated that two careful examiners can reproduce more or less identical results with the various tests at one's command. They have compared the commonly employed methods and pointed out in a convincing manner the fluctuations one may expect to find in normal subjects with each

test Their observations on the unimportance of (1) the amount of illumination and (2) the eye before which the Maddox rod is placed will do much to clarify the use of this test Their observation that "with screening the Maddox rod test uncovers more esophoria or less exophoria than without screening" is in direct contradiction to the generally accepted idea, viz, that with the Maddox rod one usually finds a higher degree of esophoria or less exophoria than with the screen and parallax test My only explanation for this discrepancy is that these tests were made on normal subjects, in whom all variations are reduced to a minimum I believe that if similar tests were made on pathologic subjects these findings would be reversed At least in my experience such has been the case A similar objection can be raised to their conclusion "The Maddox rod test gives results sufficiently like those of the screen and parallax test to be used as a replacement for it for purposes of routine testing" Since tests for heterophoria are dependent on suspension of fusion and the Maddox rod admittedly "does not completely abolish the fusion impulse," it seems to me that routine adoption of this test will necessarily lead to erroneous findings These examinations were made on subjects with muscle measurements well within the normal limits One should expect to find a minimal variation in this group, whereas if the test is used as the routine method much greater discrepancies will become manifest The use of the screen with the Maddox rod was advocated by Dolman because during World War I this situation was found to exist Several cases of high exophoria were detected with the screen and parallax test which had previously been missed with the Maddox rod test In routine office practice the Maddox rod is particularly useful in the detection of small amounts of hyperphoria and is a valuable adjunct to our equipment for muscle testing, but I, for one, am not ready to adopt it routinely, to the exclusion of the screen and parallax test

Such thorough analyses are so rare that I must congratulate the authors on their painstaking efforts and excellent presentation, from which all of us have learned a great deal I only hope that similar investigations on a group of routine office patients will soon be forthcoming

DR GLEN G GIBSON, Philadelphia Dr Scobee and Dr Green are to be congratulated on making this scientific contribution to ophthalmology in the pressing circumstances of wartime military service In my opinion, this is an important piece of work, because it focuses attention on a problem which is to become progressively more important, namely, the visual qualifications for aviation Since the objective of all is to learn the truth about tests for heterophoria, it is probably fortunate that the military ophthalmologist is primarily concerned with the best of the population in the field of ocular muscle balance, while the clinical ophthalmologist is necessarily more interested in persons at the other extreme Approaching the problem from these two extremes, one would anticipate greater differences of opinion than actually exist

The authors have carefully studied an adequate group of subjects and have correctly concluded, with due regard to the limitations of their study, that two examiners can, with this selected group, make measurements with the screen-Maddox rod test which are repeatable and statistically reliable I feel that in general this is quite true, as

day to day measurements of heterophoria probably do not vary much if the conditions of the test are repeated. Statements to the contrary in the literature refer, for the most part, to those with more pathologic cases than to patients with normal heterophoria. If screening adds only 0.3 to 0.4  $\Delta$  in the Maddox rod test to the reading without screening, I do not see the necessity of screening in the test, in which the clinical error is easily 1  $\Delta$ , as the authors prove. It is interesting and instructive that the authors demonstrate such an agreement in the screen-parallelax test and the screen-Maddox rod test. In clinical work I have not been able to demonstrate routinely such a close parallelism, particularly with the very low and with the higher amounts of heterophoria.

One wonders whether the incentive to this work was a recognition by the authors that present technics and standards of testing were excluding good men from military service. I appreciate that it is not within the province of this paper to justify the standards of the Air Corps, but, as one who is unfamiliar with military standards, I find it difficult to understand why 5  $\Delta$  of exophoria is set as the dividing line between acceptable and nonacceptable men, and I should like to ask Dr. Scobee if he would care to state whether this is a fair end point for the discrimination between subjects.

The authors have permanently established that total darkness is not a requirement and that it is not necessary to place the rod before the nondominant eye. It is reassuring to have statistical confirmation of these aspects of the testing technic.

This paper manifests the necessity of more precise definitions, classifications and interpretations in the field of muscle balance, based on a better understanding of the reflex mechanisms involved. Most textbooks consider heterophoria as a subdivision of motor anomalies, when the problem is primarily a sensory one. What one is measuring is the motor compensation for sensory conditions. Most cases of heterophoria are instances of imperfection, but they are not anomalies. There is need of more precise definition of the difference between normal heterophoria and clinically significant heterophoria.

Fusion does not perform a motor task, as the authors state. Fusion is a purely sensory process, which occurs after the fusion-vergence reflexes have produced the motor adjustment necessary to bring the eyes from the disassociated to the associated position. The fact that this is an insignificant task in the great majority of cases should be appreciated in setting standards for this subject. I feel that many of the points the authors have made will stand the test of time and will prove of permanent value, and it is hoped that these investigators will make a similar survey on patients with clinically significant heterophoria in the near future.

I wish to express to them my sincere thanks for this instructive paper.

DR WILLIAM F. BONNER, Temple, Texas. In a paper presented before the Philadelphia College of Physicians in December 1923, on "The Relation of the Weakness of the Extraocular Muscles and Depth Perception," based on two groups of patients, one with premature presbyopia and one with normal near vision, I said

In patients with premature presbyopia (1) Exophoria combined with good depth perception, (2) esophoria combined with poor depth perception, (3) orthophoria combined with good depth perception, except in cases of high latent hyperopia, in which the depth perception was poor.

In patients with normal near vision As a rule, exophoria combined with good depth perception, low degrees of esophoria combined with good depth perception, high degrees of esophoria combined with poor depth perception, and right hyperphoria combined with poor depth perception, but hyperphoria and depth perception were improved by correcting lens and prism

DR RICHARD G SCOBEE, St Louis The problem of repeating the test on "abnormal subjects" is, of course, obvious We have already tested approximately 100 patients in clinical practice, and we are beginning work on a separate group who are definitely abnormal, to see whether the test is reproducible there, as it obviously seems to be with normal subjects Certainly such a step is indicated

In answer to Dr Dunnington It was not intended that the screen-Maddox rod test should in any sense replace the screen and parallax test The idea was to show that if one takes 10 patients and ranks them in order of the decreasing degree of heterophoria, from 1 to 10, or vice versa, and if one tests these patients with the screen and parallax tests, 9, roughly speaking, will rank in the same order of degree of heterophoria, and the parallax test will uncover more exophoria than will the Maddox rod test Certainly, I should be the last to detract from the value of the screen and parallax test, which I fully agree with Dr Dunnington is the most accurate test of heterophoria available The Maddox rod test was not recommended as a substitute, but was mentioned simply for comparison If some one sends a patient to you and says, "This patient has this amount of heterophoria," and you say, "Oh, no, he has this much," you are both sincere and you are both right, but you are using different tests of heterophoria

Dr Gibson made the same point

The question was raised as to how this work began We wanted to know why the original limits were selected in the Army Air Forces, as they were, of 5 D of exophoria and 10 D of esophoria for class 1 pilots There seemed to be no good reason, and certainly I cannot suggest any answer They must have been pulled out of a hat We hope by a study of the normal to be able to predict what might be considered abnormal

**Effect of Visual Training on Existing Myopia.** DR H ROMMEL HILDRETH, DR WILLIAM H MEINBERG, DR BENJAMIN MILDER, DR LAWRENCE T POST and DR T E SANDERS, St Louis

In an attempt to improve the visual acuity, 54 selected patients with myopia were given a course of visual training, which was preceded and followed by a complete ophthalmologic examination

The technic of training, which was based on standard accepted procedures in this field, was given by an optometrist, while the pretraining and post-training examinations were made by a group of ophthalmologists

Thirty, or 55.5 per cent, of the subjects showed no change in their acuity, while 12, or 22.2 per cent, showed definite improvement, the best results being obtained in the patients with small amounts of myopia Twelve patients, that is, 22.2 per cent, showed a change so slight as to

be excluded in the results. The change in the group with improved vision averaged 27 per cent. Eleven of the 12 patients who showed improvement were rechecked at intervals of fifteen to twenty-three months after completion of training. Five of these retained their improvement, while only 1 had less than the pretraining acuity.

There was no change in the refractive error or significant alteration in the neuromuscular mechanism of the eyes. It was thought that the improvement occurred because of improved reception due to stimulation of the visual effort, as the best results were obtained in patients with a pretraining acuity less than would be expected from their refractive error, 73 per cent of this type showing improvement.

Visual training has a definite, but limited, value with some myopic patients, particularly those whose vision does not correspond with their known myopia. The effectiveness of visual training must be increased if it is to be generally applicable. Visual training merits further study from the ophthalmologist, particularly in relation to progress in treatment of myopia.

#### DISCUSSION

DR ALAN C. WOODS, Baltimore. Dr Hildreth, Dr Post and their collaborators deserve the thanks of this society for their meticulous investigation of this plaguing and perplexing problem of the value of ocular exercises in the treatment of myopia. None but the five who have labored on such an investigation can appreciate the endless and tiresome labor entailed. I congratulate Dr Hildreth, Dr Post and their associates, not only on the thoroughness and conscientiousness with which this study has been set up and executed but also on the clarity of their presentation.

My only experience with this subject has already been set forth in my report from the Wilmer Institute on a closely similar investigation made by Dr Frank B. Walsh and associates on the staff of that institution (*Am J Ophth* 29: 28, 1946).

The investigations reported here differ from the Baltimore report only in several minor respects. (1) High degrees of myopia or astigmatism were excluded, (2) a full correction to 20/20 vision was required in each eye, (3) normal muscle balance was required. In our series we took all grades of myopia up to 10 D. A full correction to 20/20 vision was not required, although this was the visual level of 81 of the subjects. Eighteen had vision of 20/30+ in each eye, 2 had from 20/50 to 20/30, and 2 had unilateral amblyopia with vision of 20/20+ in the second eye. We did not require a normal muscle balance or investigate the question of binocular vision, our investigation being conducted on the basis of improvement in the individual eye rather than in binocular vision. We tested both the pretraining and the post-training visual acuity on four charts: the Snellen letter, the Snellen number and the Snellen E chart, and a modified Landolt broken ring chart, taking as the final visual acuity the mean for these four tests. Further, in the St. Louis investigations the visual training was conducted under the direction of Dr Hildreth and Dr Post, while in the Baltimore investigation it was conducted independently by a group of optometrists and experimental psychologists, under the direction of Dr A. M. Skeffington and Dr S. Renshaw. The two courses of visual training,

however, appear to be closely similar, if not identical. Despite these differences, which I believe are unimportant, the results of the two investigations are startlingly similar.

Drs Hildreth and Post found that in 42 of their 54 patients, or 77.8 per cent, the final vision was unaffected by the visual training, while in 12 patients, or 22.2 per cent, there was definite improvement. We found no significant change in the visual acuity in 73 of our 103 patients, or in 71 per cent, while in 30, or 29 per cent, there was definite improvement. In both experiments the average degree of improvement was exactly the same—27 points in the visual efficiency scale.

On only 9 of our patients showing this improvement were we able to obtain later examinations to see whether the improvement was maintained. In 2 of these patients the improvement had been fully maintained, in 4 it had been partially maintained, while in 3 nearly all had been lost. Drs Hildreth and Post found the improvement maintained in 50 per cent of their patients showing improvement. The difference in these figures is of no statistical significance. Both the Baltimore and the St. Louis group found that the visual training had produced no change whatever in the underlying refractive error. We concluded that the improvement noted in 29 per cent of our patients was due to teaching the patient to interpret his blurred retinal images more carefully. Dr Hildreth and Dr Post concluded that the improvement occurred at the cerebral, rather than at the retinal, level—a happy phrase!

Thus, the results of these two studies are practically identical, and the conclusions drawn from them by two entirely separate groups of investigators are the same, with one exception. Drs Hildreth and Post state: "We must conclude that visual training has a definite, but limited, value with some myopic patients." We concluded, "The visual training used on these patients was of no value in the treatment of myopia." Thus, we have the paradox of two groups of investigators pursuing the same investigation, reaching results which are identical and yet drawing radically different conclusions as to the value of the visual training. I should like to defend my point of view.

The conclusion of Drs Hildreth, Post and their associates is clearly based on two facts, namely, (a) that 22.2 per cent of their patients showed improvement of 27 points in the percentage visual efficiency, and (b) that 50 per cent of these patients permanently retained the improvement. The question before us is whether these facts are significant.

In Major Pincus' paper on correlation of the unaided visual acuities with refractive errors, he specifically noted that in patients with identical refractive errors, i. e.,  $+1.50$  D sph— $1.00$  D cyl, axis 180, the vision may vary from 20/100 to 20/300, or from a percentage visual efficiency of 48.9 to one of 8.2, a range of 40.7 points. In our series, we found that patients with exactly the same refractive error likewise varied up to 42 points in the percentage visual efficiency, the mean variation being 29 points. We found, further, that when the same subject was tested with the four different charts at the same examination he might show an even higher variation, swings of over 50 points in the visual efficiency being observed on different charts. In evaluating any



beneficial results, one should, therefore, first determine whether in the pretraining determination of visual acuity the patients who showed the definite improvement had higher, average or lower visual acuities than would be expected with their refractive errors. If the pretraining visual acuity was higher than would be normally expected, any improvement obtained would be the more significant, if lower than would be normally expected, the improvement would lose its significance.

Analysis of the 30 cases in the Baltimore series and 11 of the cases in the St. Louis series in which vision improved shows that the pretraining visual acuity was the average to be expected with the refractive errors. Thus, in the Baltimore group, 7 subjects had higher than expected uncorrected vision, 16 had about the expected vision and 7 had lower than the expected vision. In the St. Louis group, 4 had higher than expected vision, 4 had the average expected vision and 3 had lower than the expected vision. If 40+ points is accepted as the normal variation in vision with the average refractive error, a swing of 20+ points in the average subject is without significance. The average improvement noted in the groups benefited by the visual training was 27 points for each series.

In my report, I called attention to the fact that the experiment was uncontrolled. This is also true of the St. Louis investigation. If the results of an experiment are negative, the absence of controls is unimportant, but when positive, these results must be interpreted against the behavior of a control group. We found it impossible to assemble a proper group of controls, and I have no doubt Dr. Hildreth and Dr. Post encountered the same difficulty. A proper control in this experiment would be an equal number of intelligent myopic patients with refractive errors and vision comparable to those in the training group. This control group should have their uncorrected vision determined, and they should be advised that patients with myopia of the same degree may have different levels of vision on the Snellen chart, depending on the care with which they interpret their own blurred retinal images. They should then be dismissed to follow their usual lives, with their vision uncorrected and with no visual training save that which they gave themselves by being more painstaking in their visual habits. At the end of training, given the test group of myopic patients, the control group should be reassembled and their visual acuities again determined, to ascertain what change, if any, had been accomplished by the simple explanation of the situation and the advice to be careful in their visual interpretations. What the results would be in such a control group, one can only surmise. I should not be surprised if 25 per cent showed an average improvement of 27 points in their visual efficiency.

In the St. Louis investigation, Dr. Hildreth, Dr. Post and their associates found that 50 per cent of patients showing improvement maintained their gain, while 50 per cent reverted to their former sloppy visual habits and lost what they had gained. In other words, 5 of 54 patients, roughly 10 per cent, showed final definite improvement. Our figures on this point are not so accurate, since we were able to recapture only 9 of our 30 patients showing improvement for the later, final, examination. However, accepting the higher, and more convincing, figures of the St. Louis group, one may well ask: Is this gain of 27

points in the visual efficiency, attained in only 10 per cent of the subjects, worth the time and the effort? This improvement corresponds to a gain in visual acuity of from 20/200 to 20/100, or, in the lower brackets, from 20/80 to 20/40. It is noteworthy that even among the trainees with the lower degrees of myopia, only 2 gained the 20/20 level, improving from 20/30.

To my mind, these meager results do not justify the expenditure of the time, the effort or the expense normally entailed by such visual training. My admiration for Dr. Post as a chairman, an administrator, an investigator and a friend is unbounded. In this instance, however, I am unconvinced. On the evidence so far advanced, I do not believe that visual training has a definite, or even limited, value in the practical treatment of myopia. It may have, in some cases, a psychologic value in reconciling the myopic person to his handicap. All in all, however, I believe that visual training should regretfully be consigned to the limbo of well intended, but fruitless, experiments.

DR. KENNETH C. SWAN, Portland, Ore. We are indebted to the speakers and their colleagues for providing us with statistical data for the discussion of a well publicized controversial problem. We can best attempt to pay our debt to these men for their tedious and intensive work by properly interpreting it to the public, to optometrists and to our colleagues.

Both authors stress that their studies were limited to visual acuity, but the training procedures described in the published report would be beneficial to patients with anomalies of convergence and accommodation. Dr. Post included no cases of such anomalies in his report, but they commonly accompany uncorrected myopia. This fact must be taken into consideration in discussing with patients visual training for myopia. For example, a young, competent attorney stated that he was receiving great benefit from visual training administered by an optometrist. It was expensive, but he was going to continue because until he had visual training he had been unable to read without glasses. Spurred by the improvement in his reading ability without glasses, this man falsely hoped to discard his glasses for distant vision. I say "falsely" because an analysis of his previous symptoms reveals that he was able to read with one eye at a time before training, but that when he attempted to use both eyes the print ran together. He had other symptoms typical of convergence insufficiency. So, in discussing visual training with one's patients, one should not be satisfied to say that visual training does not alter the refractive error. One should add that in a few cases increased visual performance may result from improved coordination of the eyes and better interpretation.

I should like to call attention to another class of patients who are not uncommon, and who fall into the hands of quacks unless properly directed to psychiatrists. These patients characteristically profess to have received great improvement in their visual acuity from training, but an objective change cannot be demonstrated. Rationalization is of no avail, for this is no simple matter of vanity concerning glasses. For example, the intelligent daughter of a university professor claimed to have obtained great improvement from expensive training received from an optometrist, but objectively I was unable to demonstrate improvement in her vision. This patient was of a schizoid personality.

This type of person expresses subconscious thoughts in a distorted form. When this girl wore her myopic correction, she saw sharply and was aware of the faces of other people. They appeared to be staring at her, consequently, with her glasses she was awkward and self-conscious. She was in a hard, sharp world of critics. Without glasses people's faces seemed blurred, but the girl was less conscious of them as individuals and felt at ease. It was a soft, blurred and kindly world. Unconsciously, this girl had accepted visual training as a means of staying in this friendly world. Rationalization and attempts to force this girl to accept the fact that she was getting no benefit from training might have done her harm. The oculist must direct patients to psychiatrists rather than drive them into the hands of quacks.

Dr Post and Dr Woods brought out the point that the improvement in visual acuity is on a mental level. The ophthalmologist uses two simple slides to demonstrate to his myopic patients the mechanism by which improvement in visual acuity occurs for a time after they discontinue wearing glasses. Experience, rather than visual training, is the deciding factor. On the first slide, any child can recognize that these simple block letters are T-H-E. The second slide shows only the shadows cast by the letters. The actual lines of the letters are missing, but the average adult mentally fills in the defects from experience and interprets the letters as three dimensional. On the other hand, the average child who has had no experience with three dimensional letters, has difficulty in reading the word. In other words, one demonstrates to the patient that with or without training he will, by experience, learn to interpret and to fill in incomplete or blurred images when he discontinues his myopic correction.

DR S JUDD BEACH, Portland, Maine. It is high time that the so-called cures for myopia by unorthodox methods be evaluated. We are indebted to Dr Post and, previously, to Dr Woods and their associates for these thorough investigations. It is generally believed that the gain is in the improved interpretation of blurred images, a position previously taken by Duke-Elder.

Though this is doubtless true of most cases studied, in last year's *Transactions* I described a different sort of case. A patient trained to squeeze his lids together was able to improve his vision during that act from about 4/200 to approximately 20/30. One keen observer thought he actually shortened the globe, another expressed the belief that the effect was simply the pinhole phenomenon.

I have since found in my office practice that this is a knack possessed only by part of the myopic patients. It is not purely the result of pinhole vision as some, while looking through a pinhole, can still further improve their visual acuity by squeezing the lids together. An 18 year old youth, whose relaxed vision was 2/60, with a 1 mm pinhole saw 6/60 in one eye and 6/30 in the other, but with the same pinhole plus squeezing he saw 6/20 in the eye with 6/60 vision and 6/20—1 in the other eye.

It will be recalled that Bates and his followers, in this country, and Simpson, in England, teach that by action of the extrinsic muscles they produce genuine shortening of the eyeball. Such a result can be conceived as effected by the orbicularis muscle. It was certainly not a pinhole phenomenon in the cases I have described. Admitting that the

improvement is mostly at the cerebral level, one should not wholly close one's mind to other possibilities

DR WILLIAM H CRISP, Denver The patient's judgment, experience and general cerebral capacity are important in visual training. Sometimes, of course, peculiar ways of thinking about things may account for the general objection to wearing myopic glasses. I had a patient several years ago who complained about the glasses that I had prescribed for her. She said, "Doctor, I cannot possibly wear these glasses because when I sit at a table I see every pore of the person in front of me." The anatomic basis that has been reported on by Dr Woods and by Dr Post and his colleagues seems to be the determining factor in a myopic patient's giving credence to the claims made by persons who charge \$175 for improving his vision.

If the patient's anatomic condition remains the same, I cannot see the ultimate advantage of these so-called exercises. A patient stated that he paid an optometrist \$175 to get him into the Army because he was not able to get in on the first test. His anatomic abnormality was just as bad as it was before, and, generally speaking, he had gained nothing toward getting into the Army.

Almost any fairly intelligent patient would gain somewhat by experience in interpreting what is seen on the test card. It is the experience of most ophthalmologists that an illiterate patient who says he does not know the letters but knows the numbers has difficulty in recognizing numbers, a difficulty which, obviously, is due to lack of familiarity with the particular shapes of the numbers on the chart, whereas he can recognize the numbers more easily if they are shaped like those with which he is familiar.

I have had a number of patients who, at the first examination and the first fitting for a myopic correction, could read down only to a certain line on the chart and who six months or a year later could read a line or two or three lines farther down the chart. Surely, some value must be given to experience of things seen which could not be seen before the correction was worn, and judgment comes into that result, just as it came into the responses of the patients reported on by the investigators today.

DR BENJAMIN MILDER, St. Louis I should like to thank Drs Woods, Swan, Beach and Crisp for their interesting and thought-provoking comments on this highly controversial, and scarcely yet touched, field.

I believe that it is possible to see in Dr Woods's comments a significant relation of the various points that he has discussed. They make it seem that, having tried this new method, and not having attained an extremely significant and highly remarkable positive result, one should therefore reject it and return, shall we say, to the ostrich attitude regarding this problem which has been prevalent in ophthalmology prior to this time.

A careful consideration of the paper read by Dr Post would indicate that our approach has been a carefully limited and highly conservative one. Such an approach explains why we limited so carefully the patients we studied in this investigation. We felt that readings for people on the fringe, at the edges of the distribution curve, might throw off our

results, so that we might get an abnormal improvement or abnormally poor results

With regard to the question of binocular vision and the evaluation of binocular vision, it should be pointed out, although that part of the paper was not read, that all the training procedures utilized by the persons performing these tests were procedures in binocularity, and therefore it is only logical that, since visual acuity as such in the average person is a binocular function and the tests were binocular tests, one should evaluate the vision of the two eyes together

I should like, further, to read a sentence that Dr Woods quoted from our paper, Dr Woods feels that the 25 per cent or so of patients showing definite improvement which was obtained both in his study and in ours has no significance in the treatment of myopia. He quoted from our paper "We must conclude that visual training has a definite, but limited, value with some myopic patients, preponderantly those whose vision does not correspond with their known myopia." I should like to read the sentence which follows "Considering the time and effort expended by the patient, the results, both in the percentage of patients improved and in the actual amount of improvement per patient, must be increased if the procedure is to be generally applicable to the routine management of myopia."

It is entirely possible that future studies will demonstrate that there is no applicability or clinical significance in this type of training in the treatment of myopia. However, when one sees oil on the ground, one usually digs for oil there, and not at some barren part of the ground where one does not suspect it to be.

Dr Swan mentioned the relation of muscle anomalies and malcorrected myopia. His point is well taken, and I believe that this would be the next logical point of departure in the investigation of the effect of visual training on myopia. I believe there is nothing unusual, or even surprising, about the success that we achieved in this investigation. All are acquainted with the fact that in amblyopia ex anopsia, which is an instance of a visual organ not being utilized to its fullest capacity, one sometimes sees with even simpler methods a much more remarkable improvement in the visual acuity.

### **Preoperative Roentgenographic Reconstruction of the Orbit.**

LIEUTENANT COLONEL E. L. SHIPLETT, Medical Corps, Army of the United States

My colleagues and I have many patients with badly comminuted fractures of the orbital and facial bones who are undergoing surgical reconstruction of the orbit. Success in this field depends to a large extent on restoration of the orbit by replacement of fragments, removal of fragments or substitution of tissue or material for lost bone tissue. The correct total diagnosis of bony deformities is shared by the roentgenologist and often is dependent on him almost entirely.

Stereoscopic posteroanterior roentgenograms, with the patient in the chin-nose position, the nose and chin resting heavily on the film, and stereoscopic lateral views, in the injured side down, are made. The films are processed in the usual way, and all are studied stereoscopically and pseudoscopically. Under stereoscopic vision the normal and abnormal bone structure is marked on one of the pair of films with an indel-

ible pencil, the normal orbit being used as a guide. After all fractures are identified and defects in the orbit created by the fractures noted and traced on the film, the film is removed and placed on an ordinary viewing box. The preliminary tracing just described is traced on the right side of the film as the patient faces the stereoscope, provided the observer is right handed, the left side of the film is traced if the observer is left handed. After this tracing is placed on the ordinary view box, which lies in the horizontal position, a piece of clear transparent paper is placed over the film and the tracing is recopied on the paper.

Our studies of reconstruction subjected to surgical control led us to certain general conclusions, with which the surgeon may or may not agree. The cephalocaudad position of the globe is important in that it might be used as an indicator for conservative or radical elevation of the orbital floor. It would certainly indicate that the same elevation is not applicable to both the high and the low-lying globe. Restoration of lost tissue, without a preoperative method of measurement, is usually too conservative. The most evident deformity is not always the chief offender as the cause of an unsightly prosthesis or malposition of the eye. Correction of the lesser of several injuries will often give a good cosmetic result which could not be obtained by correcting only the most evident injury, and a decision as to which defect to correct cannot always be determined by inspection and palpation alone. Unrecognized expansile intraorbital fractures are frequently the cause of the sunken, and otherwise misplaced, prosthesis. The size of the defect in the orbital floor is not necessarily compatible with global malposition or a displaced prosthesis, as the prolapse of orbital tissue through a small defect will cause malposition of both. It is possible that the position of the opaque prosthetic ball has some influence on the position of the artificial eye. Difficulty in attaching the superior paddle of the implant eye can be anticipated and prepared for by the simple procedure of orbital reconstruction. This procedure will aid the surgeon to measure and to shape with reasonable accuracy the tissue or material necessary for restoration before the patient is brought to the operating room.

Practical applications of this method were discovered and utilized in the surgical restoration of the wounded orbit. We believe that persistent study and consistent use of this method, or some other suitable method or preoperative reconstruction, will aid the surgeon and benefit the patient. We offer this method only as a practical aid to the surgeon, believing that it has a high degree of clinical and surgical accuracy, but do not offer it as representing in any way a physical or anatomic formula of complete accuracy. The method was developed by mutual assistance and cooperation of the ophthalmologic and roentgenologic services, and neither service could have developed it independently.

#### DISCUSSION

LIEUT COL GILBERT C STRUBLE, M C, A U S. This method of orbital tracings and preoperative reconstruction of the orbits devised by Colonel Shiflett has proved to be of extreme value in the work on orbital reconstruction at our hospital. Since its development, the procedure has been routine in all our cases prior to operation. I have chosen the term "orbital blow-outs" as being most descriptive of

many of these injuries. They occur as a result of the terrific impact produced by the modern high velocity missiles. Ophthalmologists are also seeing cases of a somewhat similar nature as a result of accidents incurred in civilian life. Enophthalmos may be so pronounced that at times only the up-turned cornea of the globe is visible. In the majority of these cases, however, the eye has been destroyed and has been removed before the patient reaches us.

Correction in these cases requires elevation and restoration of the orbital contents to their normal position and filling of the defect with either preserved cartilage or some inert material, such as tantalum mesh, as devised and developed by Dr A D Ruedemann. With tracings available, the required thickness of the cartilage, tantalum or other type of packing utilized can be estimated to an accuracy of 1 or 2 mm.

In many instances ordinary examination, including routine roentgenographic procedures and palpation of the orbital margins, has proved misleading in our attempt to evaluate the extent of injury present. Such an accurate analysis of the true extent of injury is important, since certain patients on whom a cosmetic operation might result in fatality may be eliminated from surgical consideration entirely. This was well demonstrated in 2 cases which at first appeared well suited to the usual surgical procedure. Preoperative orbital tracings in both cases, however, indicated a severe loss of bone of the posterior orbital walls, with the probability of herniation of brain tissue underneath the conjunctiva, a condition which was later confirmed by the neurosurgeon in both instances. [A case of this nature was presented.]

A surgical approach through the conjunctiva is advocated. It leaves no external scar and in our hands has proved more satisfactory than the incision through the skin. Dr A D Ruedemann, the civilian ophthalmic consultant to Crile General Hospital, devised this technic. He spent hours with us each week and gave us help and suggestions in the development of these procedures.

[Three case reports were then presented, with preoperative and postoperative photographs. The orbital tracings in these cases made before and after operation were reviewed.] In 1 case a severe fracture involved the orbital floor, the entire ethmoid capsule and the cribriform plate, resulting in complete loss of sense of smell bilaterally. At the time of the original orbital reconstruction the depressed area in the posterior superior aspect of the ethmoid labyrinth was not corrected because of the possibility of opening up the old fracture lines in this area, which extended into the anterior fossa of the skull. In spite of this precaution, some drainage of cerebrospinal fluid from the orbital incision developed, together with rather severe headaches for the first three or four days after operation. After administration of penicillin and sulfadiazine in adequate doses, the headaches disappeared and the operative orbital approach healed without further complication, with complete cessation of drainage of cerebrospinal fluid. The ultimate cosmetic correction in this case was not satisfactory because of the incomplete correction aforementioned. This resulted in some residual depression in the superior nasal aspect of the upper lid. This mild deformity was subsequently corrected by a second stage proce-

ture, which consisted in placing a curved acrylic contour stent between the orbital fascia and the orbicularis muscle, as advocated by Sugar and Forestner (*Am J Ophth* 29:993, 1946). A short 16 mm "kodachrome" moving picture was shown, demonstrating the use of orbital tracings and the operative procedure.

Colonel Shiflett, in developing this original method of orbital tracings, has made it possible for the ophthalmoplastic surgeon to approach the problem of orbital restoration with much more assurance and peace of mind than was formerly possible. The true extent and location of orbital injuries and deformities can now be accurately determined and charted prior to operation. This three dimensional tracing may be made a part of the patient's permanent record and is thus available in the operating room for reference at the time of operation. By knowing in advance the location and amount of correction required, the surgeon can proceed with the reconstruction with greater promise of success than has heretofore been possible, and by reference to such a diagram dangerous areas may be avoided. In some instances certain patients in which a cosmetic operation might result in fatality may be eliminated from surgical consideration entirely.

#### Transplantation of Human Vitreous DR NORMAN L. CUTLER, Wilmington, Del

Thirteen cases of transplantation of vitreous were reported for hemorrhages into the vitreous in 8 and for detachment of the retina in 1. The results in 4 of the former were considered successful and in 1 partially successful. The outcome in 1 of the latter was considered successful. In all cases vision returned to the preoperative level. In the cases of hemorrhage no eye had less vision at the end of the procedure. In the cases of detachment 2 eyes had reduced vision, although 1 was expected to improve.

The improvement in vision in the cases of hemorrhage with a successful result ranged from light perception to 20/50—, and from 20/300 to 20/25. Although the operation was successful in but 1 of the 5 cases of retinal detachment, all these cases were considered difficult, and operations for retinal detachment had been performed previously.

#### DISCUSSION

DR FREDERICK C. CORDES, San Francisco. As a civilian consultant in ophthalmology to the Surgeon General of the Army, it was my privilege to make observations in most of Dr. Cutler's cases, both before and after operation. In the first case it was of great importance to determine whether or not human vitreous could be transplanted successfully. From a surgical point of view the result was excellent, and but for a macular lesion, as Dr. Cutler has already pointed out, vision would have been materially improved.

Case 4 in the table was the third case in which an operation was performed, and it was probably the most spectacular. The patient was on the program for rehabilitation of the blind and, having finished his orientation training, was ready to be sent to Avon, Conn., to Old Farms, for his advanced training. The restoration of vision from 20/300 to 20/25 in six weeks was most dramatic, particularly after a period of eight months of almost complete blindness.



The result of vitreous transplantation in cases of retinal detachment has not been so good. However, in my opinion, not enough work has been done on this to justify condemnation of the procedure. The procedure may offer definite possibilities in carefully selected cases. It must be admitted, of course, that eight months, the longest interval after hemorrhage in the vitreous, does not exclude the possibility of further spontaneous clearing. Most ophthalmologists have seen cases in which as long as a year was necessary before complete absorption had occurred, and in many of these cases vision was again restored to normal. On the other hand, one has also seen cases in which at the end of that time organization of the hemorrhage had developed, together with retinitis proliferans. Experience has shown that in the latter cases little can be done once organization and retinitis proliferans have set in.

Of interest to me in these cases was the fact that for several weeks the clouded vitreous immediately surrounding the implanted vitreous continued to clear rather rapidly, while the vitreous at the periphery, away from this area, showed no appreciable change.

Further experience will be necessary before it can be determined whether or not the risk involved in transplanting vitreous is small enough to make it advisable to use the procedure in case of hemorrhage in the vitreous, with the hope that it may prevent the organization that occurs in some of these cases. In addition, it will be important to determine whether or not some method of preserving vitreous can be devised, so that it can be available on short notice in cases in which its use may be indicated.

This paper must be considered a preliminary report, and further experience will be required before the use of, and indications for, vitreous transplantation can be evaluated. However, the work done by Dr. Cutler proves that human vitreous can be transplanted, without regard to blood groups.

Dr. Cutler is to be congratulated on this piece of interesting work, which required a good deal of courage to perform.

DR. JOHN MCGAVIC, M.D., Phoenixville, Pa. It requires courage to report the first results of a new operative procedure, especially one which appears at first glance as bold as this. When a new operation is described, one can be certain that the original technic will undergo modification, that the indications will later be better defined and that there will be some resistance to the introduction of a new idea.

Ophthalmologists generally have such high regard for the vitreous that they avoid it whenever possible. We, therefore, owe Dr. Cutler our thanks for doing the pioneering work in the transplantation of human vitreous.

Dr. Cutler did some experimental investigation on animals along this line several years ago. Those who saw the eyes with which he has been working realize that they were damaged globes which had more pathologic changes than the hemorrhage into the vitreous and the detachment of the retina for which he did the transplants. I have had the privilege of seeing several of the patients in Dr. Cutler's series and have dealt with many similar patients at another Army general hospital. I assure you that these eyes tax the ingenuity of any

ophthalmologist Therefore, let us not be too critical of the visual result in these cases, but examine the technic of the procedure, its potentialities and the indications for using clear vitreous to supplant abnormal vitreous

Dr Cutler has pointed out that the blood groups of the donor are of no importance The vitreous has no metabolism of its own and reflects chemical changes rather slowly It is, therefore, rational to suppose that it can be transplanted

It may be that aspiration of multiple small, nonmagnetic foreign bodies and aspiration of parasites from the vitreous will be carried out more often now that replacement of vitreous with vitreous has been proved feasible I mention this because the incidence of foreign bodies and parasites has increased during the war, and they will be seen by many ophthalmologists in the postwar years

In describing the operative procedure, Dr Cutler mentioned withdrawal and injection of the vitreous in the equatorial region of the eyeball One might well consider using the pars plana, which is avascular, or relatively so, to lessen the danger of hemorrhage and detachment of the retina Although the lens will be close to the needle when the globe is collapsed, there should be little danger of injuring the lens, since the needle will be directed posteriorly When the retina is already detached, it would seem advantageous to inject vitreous back toward it, rather than through a new hole in the retina made by the injecting needle The pressing out of aqueous through the diathermy holes would be more effective, and perhaps more so if galvanic current, rather than the diathermy, were employed, as these holes stay open better

Dr Cutler has pointed out that attention to placing the clear vitreous in the visual axis is important In the cases of hemorrhage in the vitreous, it would be most helpful if there were some means of foretelling the fate of the blood in a given eye All have seen three types of reaction complete absorption, partial absorption with retention of fluffy, cloudlike blood in the lower periphery of the vitreous over a protracted period, and organization of blood into bands The first two types do not call for operation Perhaps if one could foretell that bands would form—and this may be due to concurrent inflammatory reaction—the transplantation could be done while the blood was still loose After the bands have formed, it is impossible to do more than clear the area between bands, and one may be afraid to do this lest the retina become detached by traction during temporary hypotony

Spontaneous hemorrhage in the vitreous in young men does not seem to me to be an indication for this procedure I saw a rather high percentage of patients with Eales' disease in the Army, and I cannot recall any who did not have spontaneous absorption, with normal vision and a normal fundus I do not refer to patients who have sustained injury or to eyes complicated by perivasculitis, uveitis or diabetes with hemorrhage into the vitreous The procedure described does not affect the underlying cause of the hemorrhage, which is not known, and would not, therefore, present the recurrence

of hemorrhage. It might result in less active absorption of blood when recurrence does take place.

Dr. Cutler reports discouraging results in cases of detachment of the retina. It should be reemphasized that these were cases of severe detachment, complicated by other factors, including previous diathermy. I believe there is reason to be more optimistic about using vitreous instead of air or saline solution. The maintenance of normal intraocular pressure is gratifying. In 1 of Dr. Cutler's 5 patients the result was spectacular. The role of the vitreous in the production of so-called idiopathic detachment is important but the mechanism has not yet been fully clarified. It will be interesting to note whether or not the foreign vitreous shrinks or remains detached from the native vitreous. One may learn as much about the mechanism of idiopathic detachments as one gains in therapy with this procedure.

To those who plan to employ this procedure, it is suggested that it be tried on animals first. Vitreous is tricky to handle, and only enough for one injection may be obtained from a donor globe. It would be embarrassing to be ready to inject donor vitreous and have something go wrong. Some of us at Valley Forge General Hospital used rabbits and utilized human eyes which had to be enucleated to develop our technic. We did not get beyond this, but we did find that we were glad to have practiced on animals and on eyes which had to be enucleated, rather than use the vitreous in clinical cases first.

We are indebted to Dr. Cutler for this fine presentation of another of his truly original pieces of clinical research. We hope that he will go ahead and will present the chemical, physical and histologic pictures resulting from transplantation of vitreous.

DR. JOHN M. MCLEAN, New York. I should like to ask Dr. Cutler to enlarge further on the advantages of maintaining that 1 per cent of normal chemical constituents of the vitreous in the material which is put back into the eye, or is put into the eye, and its advantages as compared with those of saline or other physiologic solution.

I ask this because about three years ago, at New York Hospital, I had an unusual opportunity to transfer vitreous, and I should mention that this was done at the suggestion of Dr. G. J. Bertrand, who was then resident. The patient, a man with known atrophy of the optic nerve, had an injury to one eye, with a large hemorrhage in the vitreous, which would not absorb. His other eye was completely blind from the optic nerve atrophy and had no light perception. In that patient there was the rather unusual opportunity to transfer vitreous from one eye to the other eye of the same patient. It was done in this fashion. The vitreous was removed from the blind eye first and replaced with a saline solution, then it was used to replace the bloody vitreous in the other eye, thereby eliminating the various potential difficulties of transfer from one person to another. The result was not too satisfactory, and in the follow-up examination the visual result was not at all satisfactory. In the follow-up observation of the state of the vitreous over a long period, the eye in which vitreous had been replaced with saline solution seemed to have clearer and more satisfactory media than the eye in which vitreous had been replaced by the same patient's clear vitreous. The vitreous bodies in the two eyes

were equally fluid. That is what makes me wonder whether one has an adequate chemical reason in cases of detachment for switching from injection of saline solution to that of vitreous to restore the position of the retina. Certainly, when one passes normal human vitreous through a needle even once, much less twice, one has thoroughly destroyed most of its physical properties (Friedenwald, J. S., and Stiehler, R. D. Structure of Vitreous, ARCH OPHTH 14: 789-808 [Nov.] 1935).

DR D. K. PISCHEL, San Francisco. I had the opportunity to examine 2 of the patients on whom Dr. Cutler had performed vitreous transplantation, both with retinal detachment. I examined the vitreous by means of a Koeppe flat contact glass and the slit lamp. In 1 of these patients the vitreous cavity showed no signs of any vitreous structure. In other words, it was an optically empty space, like the normal anterior chamber. I suppose that the vitreous which had been injected, as well as the original vitreous, had become entirely degenerated and liquefied, so that a uniform condition prevailed throughout the vitreous cavity.

In the second case, similar examination with the slit lamp and contact glass showed a small mass of fairly normal-looking vitreous immediately behind the lens. The posterior two thirds of the vitreous cavity, however, was optically empty, as in the first case, suggesting, again, liquefaction of the injected vitreous with a high degree of shrinkage of the original, or native, vitreous. Both eyes were quiet and showed no sign of irritation from the operation.

I should imagine, as Dr. McLean said, that any vitreous injected through a hypodermic needle would be considerably altered and, even if slightly gelatinous to start with, would be fluid after it had been injected.

The fact that the eyes stood the operation without any sign of inflammation is a favorable sign, and should lead one to think that this rather radical-sounding operation was not so radical after all and that ophthalmologists are justified in trying this new method whenever possible.

DR NORMAN CUTLER, Wilmington, Del. Perhaps I should state that I do not know the answers to some of the questions. The withdrawal of vitreous and the injection of saline solution have, of course, been performed by many surgeons. Zur Nedden reported on approximately 300 cases, although his data were not detailed enough to give one a clue to the possibilities.

It was not my purpose, in attempting this procedure, to stress the possibility of injecting vitreous rather than saline solution, rather, I wished to see whether vitreous could be injected and what the result would be. I am of the opinion that the 1 per cent protein in the vitreous is important. I do not know why, and I do not think that one is in a position to say. There are so many things about the vitreous which one does not know, except perhaps to be a little afraid of it, I feel that an attempt should be made to know more about it.

Dr McLean suggested that the effect of passing vitreous through a needle was to destroy its structure. I am sure it is not known whether that is actually so. After all, the structure is ultramicroscopic. One needs to know what happens to cause vitreous to change from a sol-gel state to a sol state.

With regard to the observations of Dr Pischel, which we were happy to have, the fact that the vitreous was injected and apparently became fluid was fairly evident, and it was confirmed in the few cases in which I was able to use a flat contact lens. What the condition of the vitreous was before other vitreous was injected I do not know. It was certainly abnormal, but how fluid it was could not be determined. Whether the viscosity of the vitreous can be maintained after it is subjected to some trauma, which is present in a transplantation procedure, remains to be determined. I was, of course, careful to point out that this was not my hope in this procedure, in fact, some of the vitreous which I injected was fluid at the time I injected it.

#### FOREIGN BODIES OF THE GLOBE A SYMPOSIUM

**Pathologic Aspects** MRS HELENOR CAMPBELL WILDER, Washington, D C

Retained foreign bodies were found in 731 of 3,882 eyes of soldiers studied at the Army Institute of Pathology during World War II. All globes with penetrating wounds were examined roentgenologically and were searched for foreign bodies. In many instances the particles were so small or so deeply embedded in organizing hemorrhage or inflammatory membrane that they were not recovered from the gross specimens and became visible only on microscopic examination. These could not be subjected to the magnet test, but sections containing them were stained with prussian blue. The particles which gave a positive reaction for iron were classified as probably magnetic, although the degree of their magnetic quality could not be determined, whereas those giving no reaction were regarded as nonmagnetic. In many eyes the particles were multiple, and in a few both magnetic and nonmagnetic materials were observed.

The nonmagnetic foreign bodies comprised a variety of materials. Among the metal substances, copper, brass, lead, nickel and zinc alloy were identified, among the nonmetallic, glass, vegetable matter, eyelashes, rock, shale and clay predominated.

Abscesses were frequently seen around the sites of foreign bodies of various types, being almost invariably present around vegetable matter. In the vitreous chamber the subsequent formation of a pyogenic membrane resulted in retinal detachment and phthisis bulbi. Foreign body granulomas appeared around all kinds of foreign bodies, but the formation of giant cells seemed to be stimulated particularly by eyelashes and vegetable matter.

Sympathetic uveitis developed in 5 eyes with retained intraocular foreign bodies. A variety of infections followed introduction of foreign material into the eye. Masses of cocci, bacilli and unidentified fungi were sometimes seen in abscesses in the vitreous.

The paper was illustrated with thirty-five lantern slides.

**Experimental Work on Intraocular Foreign Bodies.** LIEUTENANT COLONEL G C STRUBLE, Medical Corps, Army of the United States

The author's method of removing magnetic foreign bodies from the eye with the Lancaster magnet was published in the *American Journal of Ophthalmology* (29:151-161 [Feb] 1946). Further clinical experience and experimental studies, using the Lancaster hand magnet with a foot switch, were made to determine the reaction of metallic foreign bodies to the magnet current within the eye. Experiments were carried out on eyes of freshly killed hogs less than twelve hours dead which were kept refrigerated. Observing the metal particles in the vitreous under magnetic attraction showed that success of the operation on the first application of the magnet depended on the initial impact of the foreign body against the inner layers of the globe. Larger fragments were delivered without difficulty. Small fragments 0.25 mm and less in size had to be aided in their path through the uvea.

Foreign bodies were experimentally planted in the retina and the choroid, and efforts to remove them with a magnet were made in the usual manner. Where the fragment was pulled laterally for a distance of 3 or 4 mm toward the sclerotomy opening and magnet, a tear or gutter in the retina or choroid was created throughout the length of the movement of the particle. When the foreign body was embedded in the choroid or the retina directly overlying the scleral opening, it was always pulled through by the magnet on the first attempt, with a minimum of trauma. This observation is further argument for precise, pinpoint localization of a metallic foreign body embedded in these structures at the time of surgical removal.

Small particles free in the posterior portion of the vitreous can be brought forward temporarily but retract into the vitreous as the current is turned off. None could be drawn into the anterior chamber, and none would become embedded in the ciliary body. Particles 1 mm in size and larger could be consistently brought forward. They would move slowly but could be embedded in the ciliary body or drawn into the anterior chamber.

Concerning magnetic foreign bodies in the retina, particles of less than 1 mm in size were not disengaged from the retina, but those 1 mm and over were suddenly disengaged and moved rapidly through the vitreous toward the magnet. The larger the particle, the greater the impact on intervening tissues. All particles except those 0.25 mm in size caused some separation of the retina.

Attempts to remove particles planted between the retina and the choroid were unsuccessful if they were less than 1 mm in size. Particles 1.5 mm or larger could always be delivered. The larger the foreign body, the more rapidly it would perforate the retina. Disengagement was always sudden and under great tension.

Foreign bodies placed between the choroid and the sclera were most difficult to remove. Particles 1 mm and less in size could not be removed, but particles 1.5 mm and over produced an increasing degree of choroidal separation and retinal elevation. In no instance were the choroid and retina perforated or the foreign body delivered.

It was realized that many factors existed in these experiments that do not exist in the human eye. The author stated, however, that given

the problem of removing a foreign body, with identical equipment available, it is logical to assume that the results obtained experimentally represent the best which can be expected

### **Roentgenographic Localization of Intraocular Foreign Bodies** DR W H DROEGEMUELLER, Chicago

To us, as ophthalmologists, the problems in the localization of intraocular foreign bodies involve more than the purely technical aspects of the methods of localization now available. The roentgenologic technics of localization and the calculations used are highly perfected, with little call for improvement unless it would be in the better visualization of the less opaque foreign bodies. However, the ophthalmologist, in transposing the position of a foreign body from the roentgenologist's chart, is subject to more or less error. Whether the Sweet method, the Comberg contact lens technic or markers of various types sutured to the exposed portion of the eye are used, the basis for the localization is the relation revealed between the foreign body and the orientation-marking device, which has a known position to the eyeball proper.

The checking of the primary localization can be accomplished by a method described by Colonel Struble in 1942 as pinpoint localization. Absolute localization is essential in any attempt to remove a nonmagnetic foreign body, and usually the first attempt is justified only after a careful consideration of the findings in the localization procedure. In the usual cases of magnetic foreign bodies, in which magnetic power can make up for inaccuracies of localization, the recovery of the foreign body must be considered in the light of the trauma produced in the extraction. An argument in favor of accurate localization is the hypothesis that the least traumatizing pathway of removal would be directly out of the eyeball, without the production of any lateral drag on the retina or the choroid. But this is a hypothesis, and there are no cases in which the foreign body could be drawn away from the retina with less harm than through it. (By means of lantern slides the author illustrated several methods of localization of foreign bodies by use of specially applied markers attached to the eyeball. The Berman localizer reveals the pressure of magnetic and some of the larger nonmagnetic fragments by an intensity sound signal. It is not as sensitive as the roentgenographic method.)

Parallax studies and the technic of injecting air into Tenon's capsule, as described by Spackman, deserve special mention. The latter procedure is of use in determining whether a foreign body is intraocular or extraocular. The routine use of stereoscopic plates has a definite value. The ophthalmologic problem in roentgenologic localization of foreign bodies is in critically evaluating the technic used and in considering the probable trauma to the eye in the process of extraction.

### **Surgical Removal of Intraocular Foreign Bodies** DR TRYGVE GUNDERSEN, Boston

A silhouette of the human body covers a surface of about 4.2 square feet (3.9 square meters). The extremities occupy about 35 per cent of the area of the silhouette, the head and neck, about 13 per cent,

and the eyes, about 0.1 per cent. Nevertheless, the percentage of battle injuries of the eyes is ten to fifteen times as high, owing to the fact that a small abrasion of the cornea will cause a soldier to be evacuated. In the eighty-four hospitals in the African and European theaters the cases of ocular injuries constituted about 2 per cent of the hospitalized patients. In the entire war, about 1,400 Army and Navy service men were made blind by battle injuries.

Some new features of ocular injuries were learned in the war. The velocity of fine fragments was found to be much higher than in the first world war. A single wound of entry with multiple intraocular foreign bodies was thought to be due to molten metal. New instruments for location of foreign bodies (Berman, Carney) were introduced. Magnets of various types (Lancaster, Mellinger and others) were used extensively.

Factors which influence the choice of operation for intraocular foreign bodies are the amount of damage to the eye, the nature of the foreign body and the possibility of removal of the foreign body. Because of the difficulty in determining damage to the eye borderline injuries should be observed for a time before enucleation is decided on. Severe hemorrhage into the anterior chamber usually becomes associated with glaucoma and calls for early removal of the eyeball. Foreign bodies differ tremendously in their toxicity. Gold, silver and platinum are tolerated fairly well, lead and zinc, less so. Soft iron and copper, and particularly brass, are tolerated poorly. "Plexiglass" seems to be relatively inert.

Practically no intraocular magnetic foreign bodies defied removal with the modern methods of localization and approach. Nonmagnetic foreign bodies require meticulous localization. They can be removed with ingenious devices, such as Thorpe's endoscope or under direct observation. Both the anterior and the posterior route were used for removal of magnetic bodies. The anterior route, when feasible, was considered safer.

#### **Reconstruction of the Eyelid** MAJOR ARTHUR E. SHERMAN, Medical Corps, Army of the United States

From the summer of 1944 to the spring of 1946, nine of the Army general hospitals in this country were designated as centers for plastic and ophthalmic surgery. Of the large volume of casualties evacuated to these centers for reconstructive surgery during that period, each center handled from 300 to 400 requiring ophthalmic reconstruction. In some of these hospitals this type of surgery was the function of the ophthalmologic service, in others, of the service of general plastic surgery.

Certainly, all of us who did much of this work are indebted to the late Dr. John M. Wheeler for the methods and principles which he developed and advocated. For vertical full thickness scars of the eyelid with notch deformities at the margin and for small full thickness loss of an eyelid, Wheeler's halving repair was the procedure of choice. For loss of skin from burns or lacerations, with resulting cicatricial ectropion or lagophthalmos, no better method of correction was found than that used by Wheeler, with the use of intermarginal lid adhesions, proper preparation of the bed for skin



grafting and the use of full thickness skin from the upper eyelid or posterior auricular skin for the graft

All degrees of full thickness loss of the upper or lower eyelid were encountered. For loss of a large part of the tarsal portion of an eyelid, Dr Wendell Hughes's method of reconstruction was very useful. In repair of some of the more extensive losses, it was necessary to use sliding skin flaps as a preliminary procedure, before joining the eyelids according to the Hughes method. Moderate or extensive loss of bone of the orbital margin was replaced by cancellous bone graft from the ilium. In some of these cases it was also necessary to enlarge the orbital socket with mucous membrane grafts. A number of illustrative cases were discussed, together with the methods used for reconstruction.

#### DISCUSSION

DR EDMUND B SPAETH, Philadelphia. Dr Sherman has had a tremendous clinical experience in ophthalmic plastic surgery. I have seen some of his results, and it behooves us to profit from them. Differences of opinion are natural—perhaps even healthy. My discussion, while it expresses a difference of opinion on some points, in the final analysis simply supplements and emphasizes certain of his statements.

As to his dislike of the use of pedicle flaps, I see no way out of their use in certain cases. Underlying disease of the osseous structures and the presence of deep cicatrices make it almost impossible to utilize, with full satisfaction, free skin grafts, of either the razor-cut or the full thickness type. Dr Sherman calls attention to his satisfaction with the use of supraclavicular skin—almost any amount of this can be easily and safely transplanted by means of a delayed transfer pedicle flap from that area to the region of the eyelids. Even greater, however, is his dislike of pedicle flaps from the immediate neighborhood of the eyelids. Given a patient with an intact eyeball and with an extensive deficiency of the conjunctiva, there is no better way of making the two transplantations simultaneously than that of lining a pedicle flap first with the mucous membrane and then transplanting both to the new position.

Slide 2 answers the problem of repair of loss of bone as the result of osteomyelitis, now quiescent, and sequestrectomy. Also, it shows my preference for the use of cartilage, in this instance an autogenous graft, though cadaver cartilage might have been as satisfactory, in contrast to Dr Sherman's preference for cancellous bone from the ilium. Frankly, I have discontinued the use of autogenous bone grafts wholly, and for at least five years. This may be an error on my part, but it seems that the cartilage grafts have done as well.

I agree wholly and without equivocation with Dr Sherman's statement in regard to pressure dressings and his disagreement with Brown in this respect. The sutures that Brown has used are not only unnecessary but unwise. They must be introduced, they must be removed, they are a wick for low grade secondary infection of the graft, they cause additional scarring, and they limit the size of the graft possible. They give a pressure dressing, to be sure, but one less satisfactory than that obtained with a mold of dental stent or

dental wax fitted to the site for the graft or grafts immediately prior to their placement in position

Again, Dr Sherman emphasizes the necessity of intermarginal adhesions with free skin grafts to the eyelids. I agree to this without argument when both the upper and the lower lid are corrected simultaneously. When, however, the upper lid only needs correction and the conjunctiva is adequate, intermarginal adhesions are not necessary.

Slide 3 shows such a case. It illustrates the ectropion residual to severe herpes ophthalmicus necroticans. The patient was blind in her opposite eye, and intermarginal adhesions would have limited her vision seriously during the process of recovery. The same objection applies to an isolated correction for ectropion in the lower lid if similar circumstances are present. Temporary intermarginal sutures must be employed during use of the postoperative dressing to protect the cornea from damage, but as soon as the dressings are permanently removed the sutures can also be removed.

Dr Sherman gives credit to Dr Wendell Hughes for a principle in total reconstruction of the eyelid which I also wish to mention. A tremendous amount of credit properly belongs to Dr Hughes for the reconstruction he has done in these difficult cases. It in no way detracts from this credit to call attention to the fact that the underlying principles of this procedure were first presented by Landolt and subsequently extended considerably by Axenfeld. This criticism may seem trite, but it is proper. It was a pleasure to discuss this paper, and I compliment Dr Sherman on his beautiful work.

DR JAMES N GREER, Washington, D C. The Army Medical Corps has, indeed, been fortunate in having available men with such thorough understanding of ophthalmic plastic surgery as Major Sherman's work so ably demonstrates. All are agreed as to our indebtedness to the late Dr John M. Wheeler for the principles of this branch of surgery. Dr Wendell Hughes has made a valuable contribution to reconstructive surgery of the lids, and the procedures advocated by him have proved extremely useful, especially when there has been extensive damage to one of the eyelids.

It has been my experience that there is more redundant skin on the eyelids of old people, thus making the procedures advocated by Hughes much more feasible than in the case of younger persons.

It is essential that uniform pressure be maintained over the grafted area in any plastic procedure. This is particularly true when free grafts are used. It is especially difficult to maintain such pressure after grafting an eyelid if enucleation has previously been performed. The method of applying pressure, as advocated by Dr Barrett Brown, yields excellent results in such cases. Dr Brown's procedure is to leave long the sutures around the margin of the free graft, tying these over mechanic's waste so as to produce uniform pressure.

There is certainly no more adequate operative measure for correction of notching of the lid margin than Wheeler's halving operation.

I should like to emphasize the importance of early treatment and care of severe injuries to the eyelids. Owing to the greatly increased activity of the air forces and the motorized units of troops in the recent war, there were large numbers of patients with severe burns of the

face These patients were given emergency treatment in evacuation or station hospitals and soon were returned to general hospitals, where they received definitive care It is generally recognized that the most serious sequela of such an injury is damage to the eye from exposure This was inevitable unless preventive measures were instituted at an early stage In order to forestall cicatricial ectropion, with resultant exposure keratitis, one of two procedures was generally carried out in the general hospitals in the European Theater of Operation

As soon as severely burned lids began to granulate, a split thickness skin graft was placed over the raw surface, this served as a dressing graft and prevented extensive contracture of the lids A dressing graft may be taken from another person, in which case it serves for a limited period only Such a graft was necessary in exceptional cases in which it was felt that further loss of skin would be detrimental to the patient This procedure was helpful, and no doubt it was responsible for preventing serious damage to the eyes of many patients Even if the patient was most severely burned about the face, there was seldom serious damage to the lid margins, therefore, intermarginal adhesions were feasible in these cases The formation of these adhesions at an early stage prevented the severe cicatricial ectropion which was certain to develop This procedure could be followed by early grafting if extensive damage to the skin and subcutaneous tissue predicted extensive cicatricial contracture as an end result These temporary grafts could be replaced by more suitable skin later if need be This method proved to be eminently satisfactory and provided adequate protection to the eye

In most instances cicatrization could take place and a suitable skin graft to the lids be made at a later period, the eye having been well protected in the meantime

Many of the patients receiving such severe burns of the head had no available skin on the eyelids or the postauricular area for covering the eyelids as a final operative measure In such cases free grafts from the supraclavicular area proved to be satisfactory It was found that early repair of damage to the eyelids would in many instances save the patient weeks of hospitalization Even when there was loss of more than one third of the eyelid, the defect could be corrected by utilizing the sliding flap from the temporal side This could be carried out as a primary measure or after debridement and secondary closure, even though a period of from three to five days had elapsed since the original injury to the lid This procedure was particularly applicable to injury to the lower lid

If such complete repair of injury to the eyelid was not feasible, a marginal suture was placed wherever possible in order to preserve the lid margin This was a distinct aid in subsequent reconstruction of the lid

In reviewing the recent literature dealing with surgery of the eyelid, one is impressed with such expressions as "marked tendency to tissue separation and frequent recurrences of the initial defect" Such an occurrence should be rare if one of the most important principles of plastic surgery is observed, that is, that the suture lines should never be closed under tension

DR ARTHUR E SHERMAN, Newark, N J There would, of course, be a difference of opinion as to some of these procedures I did say in my paper that one should avoid pedicle flaps if at all possible I did not mean that there are not at times cases in which one must use them

With regard to bone grafts and cartilage grafts, again, there is great difference of opinion My associates and I used cartilage grafts, both autogenous and preserved cartilage, and we were not as well satisfied with the cartilage as with cancellous bone from the ilium I feel that the advantage of cancellous bone is that it is easily shaped to fit the defect Within two or three weeks it is firmly attached, that is, it has grown fast to the adjacent bone, and within another month or two the bone graft has been covered with a pseudocortex The absorption of the graft is negligible

I have never felt that dental stents should be used with a full thickness graft on the eyelid, but there is difference of opinion with regard to that

I still believe that lid adhesions are extremely important if one wishes to obtain the most uniformly good or excellent result The adhesions serve an important purpose in that during the period from about the second to the eighth week after operation these full thickness grafts, or Thiersch grafts, will tend to contract, but, with the constant pull of the opposite lid, through the adhesions, the grafts will become smooth and fine textured, so that at the end of three months, when the adhesions are cut, the graft is usually the size it was originally and there should as a rule be no residual slight ectropion I realize that Dr Hughes's operation is a modification of older procedures, but it is a definite modification I believe that it is more useful than some of the older procedures, although there are times when some of the older procedures have their place

With regard to Dr Brown's method of using pressure on the eyelid, that, again, I think is simply a modification of the Gillies form of dressing, in which he used an epithelial "outlay" In the hands of such surgeons as Dr Brown, the method usually yields fairly good results, though I believe less uniformly, certainly, the average ophthalmic plastic surgeon does obtain much more uniformly good results by following Wheeler's perfected procedure

I am glad that Dr Greear brought out the use of lid adhesions and that of the Thiersch graft in the immediate care of these burns overseas I can recall several men who were evacuated to us on whom nothing more than one or two lid adhesions on each side had been produced, and who three months from the time they were burned, required no additional skin grafting All that one had to do was to cut the lid adhesions and the lids were perfectly normal

**Roentgen Therapy of Retinal Diseases Characterized by New-Formed Blood Vessels (Eales's Disease, Retinitis Proliferans):**  
A PRELIMINARY REPORT DR JACK S GUYTON, Baltimore, and  
DR ALGERNON B REESE, New York

This article will be published, with discussion, in a later issue of the ARCHIVES

# Marginal Corneal Infiltrates and Ulcers DR PHILLIPS THYGESON, San Jose, Calif

Simple catarrhal ulcers and infiltrates were the commonest type of corneal disease observed in this study of 200 cases of marginal ulcer. Although usually benign, the ulcers were sometimes severe and recurrent, leading to cicatrization extending into the pupillary area or to irregular astigmatism. They were almost always associated with chronic catarrhal conjunctivitis, usually staphylococcic, but in a few cases caused by other such agents as the diplobacillus of Morax and Axenfeld, the nonhemolytic streptococcus and coliform bacilli. In 2 cases ulcer was associated with vernal conjunctivitis, and in 1 case it was an allergic reaction to a local anesthetic. Coincidental blepharitis was an almost constant feature of the cases of the staphylococcic and diplobacillary type. Marginal catarrhal ulcers were also associated with acute catarrhal conjunctivitis caused by *Staphylococcus aureus* and by the Koch-Weeks bacillus (*Hemophilus conjunctivitis*). In 4 cases the ulcer occurred coincidentally with gonorrheal arthritis and was presumably secondary to metastatic gonorrheal conjunctivitis. In 8 cases it was secondary to chronic conjunctivitis for which the cause could not be found.

There were 14 cases of ring ulcers and infiltrates, which, with 2 exceptions, appeared to be endogenous, occurring in association with gonorrheal arthritis, bacillary dysentery, influenza, periarteritis nodosa and lupus erythematosus. The 2 exceptions were cases of severe staphylococcic conjunctivitis with multiple marginal ulcers which coalesced to form ring ulcers.

There were 6 cases of chronic serpiginous (Mooren's) ulcer, typical in clinical appearance and course. There was no associated conjunctivitis in these cases and, so far as could be determined, no relation to any systemic infection. Careful laboratory studies of smears, scrapings and cultures failed to reveal any significant micro-organisms, and animal inoculations all gave negative results.

Prophylaxis of recurrent marginal ulcer of the catarrhal type is believed to be entirely a matter of controlling the chronic conjunctivitis. This, in turn, is largely dependent on control of the chronic blepharitis, either staphylococcic or diplobacillary, which in most instances was found to be the primary focus for both the conjunctivitis and the keratitis. No information of prophylactic value was obtained in connection with either the ring ulcer or the chronic serpiginous (Mooren) ulcer.

Treatment of catarrhal marginal infiltrates and ulcers appeared to consist entirely in treating the primary conjunctivitis and blepharitis. Except in rare instances, local treatment of the ulcer was unnecessary. *Staphylococcus toxoid* proved to be of value in preventing recurrence of catarrhal ulcers, even when cure of the primary conjunctivitis was not obtained. Treatment of ring ulcers and infiltrates was also directed toward the primary cause, which was almost always a systemic disease. Local treatment was found to have little value, and cauterization of the ulcer seemed only to aggravate it. In the treatment of chronic serpiginous (Mooren's) ulcer the sulfonamide compounds and penicil-

lin were ineffective. Delimiting keratotomy and repeated paracenteses were apparently successful in arresting progression in 3 of the 6 cases.

No evidence was obtained to indicate that riboflavin deficiency contributed to the development of marginal ulcer or that treatment with riboflavin was curative.

No true example of marginal keratitis due to acne rosacea was seen in this series. There were 9 cases of rosacea with typical catarrhal marginal ulcer, but in these cases the ulcer was believed to be due to secondary staphylococcic infection.

#### DISCUSSION

DR C L SCHEPENS, Brussels, Belgium. I congratulate Dr Thygeson on his excellent paper. Personally, I learned a great deal from it.

The geographic distribution of corneal infections due to the Koch-Weeks bacillus is of interest. It was frequent in Western Europe thirty years ago. Nowadays, it has practically disappeared. I believe that at Moorfields Hospital (London) there has not been a case in fifteen years. Personally, I have never seen a case in Brussels. The same comment applies to vernal conjunctivitis, which is frequent in Spain but is seldom met with in Belgium, Netherlands or France.

It has been stated that penicillin is not active against the diplobacillus. I believe that some authors have found it active (F A Juler, London, and others). Perhaps further investigation will have to be made on this particular point.

I have never had any striking results with vitamin A, thiamine, riboflavin or ascorbic acid. I have used vitamin A locally and in intravenous injections. One has to be cautious with the injections, which sometimes cause diarrhea. I have tried intravenous injections of riboflavin, following the advice of Williamson-Noble (London), but with no favorable results. Intravenous injections of 500 mg of ascorbic acid, every other day for about two weeks, appeared more satisfactory.

One point of importance is the advisability of using atropine in every case of corneal involvement. It has been said that it is not necessary to use atropine in certain cases of corneal ulcer. This is contradictory to the teaching in many European universities. I believe the classic teaching is that atropine should be used when there is corneal involvement. If no atropine is necessary, it means a substantial shortening of the period of incapacitation. The advisability of using atropine depends, in many cases, on whether or not one believes that it has a favorable action on the nutrition of the cornea.

I agree with Dr Thygeson that cauterization is sometimes done much too freely. In cases of stubborn corneal ulcer, it often does more harm than good.

In a difficult case of marginal ulcer, the following therapeutic means are worth trying, although they are not always successful. First, some marginal ulcerations heal more quickly with physostigmine than with atropine. Second, local applications of ultraviolet rays may be useful. The effect is enhanced if 1 per cent fluorescein sodium is instilled immediately before the light treatment. Third, the local application of beta rays by means of 10 mg of unscreened radium sometimes gives good results. Fourth, small doses of roentgen radiation may also be used. One applies locally between  $1/3$  and  $1/50$  of erythema dose every

other day for six to ten days. This method sometimes gives good results in cases of ulcers following acne rosacea and in cases of Mooren's ulcer.

The general health of the patient must be cared for and much attention should be paid to his diet and to whether he takes enough fresh air. If the patient does not do well I like to take him to the hospital at an early stage, for general rest is important. I give him milk injections, and if he does not improve I do a tarsorrhaphy. I believe this operation is of value in every difficult case of corneal ulcer. I prefer it to a conjunctival flap, for one does not see what happens under the flap and in some cases the flap remains permanently adherent to the ulcerated cornea and has to be removed surgically after the ulcer is healed.

I am not in favor of paracentesis unless the tension is high. As a general rule, when there is a bad ulcer, I avoid surgical intervention on the cornea proper.

DR JAMES H. ALLEN, Iowa City. My experience with marginal lesions of the cornea has been similar to that expressed by Dr. Thygeson. However, there are some points on which he and I differ, and I should like to speak about a few of these, as well as some on which we agree.

I think that staphylococcal marginal ulcers of the cornea should not be taken lightly, for several reasons. One is that I saw an eye destroyed by a lesion which began as a simple staphylococcal marginal ulcer and spread, formed a ring ulcer and produced central necrosis of the cornea, with rupture of the cornea and loss of the globe. That occurred in the days before antitoxin was used, and before sulfathiazole and penicillin were available.

However, another reason for not taking these lesions lightly is that at times they undergo exacerbations even under treatment, and one must not administer toxoid without caution. If one is dealing with a staphylococcal marginal ulcer of the cornea, it is better to give antitoxin until the ulcer is healed before beginning active immunization with toxoid.

I should like to show slides from 2 cases of staphylococcal marginal ulcer of the cornea. Infiltrations are seen at the upper nasal margin. The surface is ulcerated over these infiltrations. The patient was given 10,000 units of staphylococcus antitoxin intramuscularly daily for four days, with the result that the ulcerations healed rapidly. She was later immunized with staphylococcus toxoid, and no recurrences developed.

There is importance in emphasizing antitoxin treatment, even though penicillin is available. Dr. Thygeson has reported from his experience that 20 per cent of ocular strains of staphylococci do not respond to penicillin therapy. I can support that statement. However, it is my impression that more than 20 per cent of ocular strains of staphylococci are not affected by penicillin, therefore, antitoxin therapy should be considered if penicillin is not giving results in the treatment of staphylococcal marginal ulceration of the cornea.

I have seen numerous cases of superficial punctate epithelial keratitis as a result of vernal conjunctivitis, particularly the limbic variety, but I have not seen marginal corneal ulcer or central corneal ulcer with vernal conjunctivitis except in cases of secondary infection. In

a case of a youngster, severe marginal keratitis with ulceration was superimposed on limbic vernal conjunctivitis after he had been vaccinated

My experience with acne rosacea has been similar to that of Dr Thygeson. The ulcerated lesions have always yielded pathogenic organisms.

DR PHILLIPS THYGESON, San Jose, Calif. I wish to thank the discussers for their valuable comments, and I should like to discuss one or two of them.

Dr Schepens mentioned atropinization. I have felt that in cases of simple marginal ulcer with little irritation of the iris the incapacity caused by the atropine outweighed the advantages. I have frequently substituted homatropine for atropine in such cases.

Dr Schepens' experience with the Koch-Weeks organism in Europe has paralleled mine in this country. In my experience, the Koch-Weeks bacillus in conjunctivitis of epidemic form has been encountered only in Florida and California. I actually saw no case of this infection in New York in a period of about six years, although Dr Weeks made his original studies on the organism there.

I shall certainly try roentgen rays and radium in treating Moooren's ulcer, in view of my only partial success with other methods.

Time prevented me from discussing the shock therapy of ulcer. It proved of definite value in my series of ring ulcers.

Dr Allen's work on staphylococcus antitoxin in treatment of staphylococcal ulcers is outstanding. It is true that penicillin-fast organisms will become more frequent, and, whereas new antibiotics may be developed, it is certain that there will always be cases in which a staphylococcus antitoxin will be of great value.

**Nonperforating Ocular Injuries in Soldiers** DR BENJAMIN RONES  
and MRS HELENOR CAMPBELL WILDER (by invitation), Wash-  
ington, D C

This report dealt with 104 cases of nonperforating ocular injuries in soldiers. Forty-seven eyes were injured during combat or training. The interval between injury and enucleation varied from less than one day to two and one-half years. In these eyes hemorrhage was the condition most frequently encountered although nonpurulent endophthalmitis, detachment of the retina and secondary glaucoma also were often noted. Injury to the eyes of 57 soldiers had preceded induction into the Army. The shortest interval between injury and enucleation in this group was four years and the longest twenty-eight years. Chronic endophthalmitis was the most frequent lesion, with cataract, detachment of the retina and choroid, and secondary glaucoma following, in that order. A great variety of degenerative and late inflammatory changes were recorded.

An inflammatory reaction was present in 20 cases in which no operation had been performed. Purulent endophthalmitis in 2 of these cases had resulted from intraocular extension of purulent keratitis. A granulomatous inflammatory reaction was observed in the ciliary body and processes in a third case. The most striking cellular response was observed in a fourth case, in which there was active endophthalmitis, with dense lymphocytic infiltration around Schlemm's



canal and chronic inflammatory cell infiltration in the iris, ciliary body, retina and nerve head. This reaction was regarded as a response to infection. In the remaining 16 cases the inflammation was clearly a response to tissue trauma and subsequent hemorrhage, although in 2 cases the number of eosinophils in the infiltrate suggested an allergic factor. The inflammatory process was chiefly in the anterior segment in 12 cases and in the posterior segment in 2 cases. The paucity of the cellular response was noteworthy, lymphocytes and plasma cells were the dominant types. On the other hand, the exudative response was pronounced and resulted in the formation of anterior and posterior synechiae, together with pupillary and cyclitic membranes.

#### DISCUSSION

DR W I B RIDDELL, Glasgow, Scotland. In opening the discussion, it is difficult not to become lost in details of particular cases. When I heard that I was to take part in this discussion, I had only the title of the paper, and I wondered what I could contribute that might be of interest and bring a slightly different point of view to the consideration of the many problems which arise from this material.

It seems to me that the general military experience in the British army is similar to that in the American army, with no racial discrimination with respect to booby traps or grenades, but there is a difference in the injuries occurring in British civilian air raids because there destruction was indiscriminate, that is, the age groups represented the whole population, and the sexes were affected equally. One should not keep this in mind when considering the material at Washington, since these ocular injuries respond differently in older age groups than in younger ones and there might well be a sex difference also. One is aware of the remarkable sex difference in Eales's disease, which occurs predominantly in young men.

Another difference in the civilian ocular injuries was the enormous excess of those due to glass. In the large majority of cases in the heavy raids, the eyes were badly damaged or destroyed by flying particles of glass. The tissue reactions which my colleagues and I saw were mainly intraocular hemorrhages. We did learn to what a remarkable extent an eye can withstand a spicule of glass, the glass coming out and the eye being repaired. The injury does require surgical treatment.

One of the difficulties was that these civilian injuries were not emergencies. They were dealt with by general surgeons, and the patient might lie for twenty-four or forty-eight hours before any one discovered that there was anything wrong with the eye or that anything, in fact, could be done for him.

I recalled that before the war one of my colleagues, Dr A M Wright Thomson, had wondered about the effect in eyes damaged in crush injuries. He is a careful observer, and negative findings are not always made by a careful observer. He collected 11 cases of crush injuries. These were mostly cases of young people who were crushed in elevators or between roller bands, that is, their chests and bodies were crushed. They all had subconjunctival hemorrhages. Many of them had subcutaneous hemorrhages around the eyelid, but of the 11 cases there was only 1 in which a strip hemorrhage was observed.

in the retina That negative finding occurred to me to be of importance, because it shows that an injury around the globe or its adnexa is required to affect the globe itself About half the patients recovered, and in none of them did any injury to the bursa, psychiatric disturbance or arthritis develop That point struck me as I was listening to the presentation of the paper by Dr Rones

When I looked at the material before the paper itself was presented, an amusing idea struck me, and I considered it more carefully I thought it might be valuable in presentation not only of this material but frequently of clinical material if one divided the cases into arbitrary categories of one week, three months, a year, three and one-half years, and so on, presenting it in tabular form and concealing certain information, which might be brought out by a mathematical device If there is one thing the armies and the government service in both Britain and America inquire into carefully, it is the report They are always looking for dates and such things I am quite sure that Dr Rones knows the day of injury and the precise day of removal of the eyes If one counts up the total number of days, calls the day of injury zero, or V-Day, ten days later, V plus 10, and so on, one may then use the logarithm of the days and get categories in which one can place the material, thereby spreading out the tabular material I don't know whether I have managed to put that idea across to you Perhaps you may think it is a silly sort of idea, but the table which Dr Rones has in the text of his paper suggested it to me and it is a convenient and useful device for any series of clinical observations covering a long period Arranged in any other way, the material makes an enormous table, which nobody can understand and few people read

Another matter which came to my mind was the point brought up by my senior assistants, Dr I C Michaelson and Dr George I Scott In those days they were Brigadier Scott and Major Michaelson They wrote a paper which appeared in the *British Journal of Ophthalmology* (30:42 [Jan] 1946), dealing with 301 battle casualties, in 47 of which the injury was nonperforating, similar to those of Dr Rones and Mrs Wilder They made a point which I think is of interest in considering material of this kind They suggested that there is a difference between an air-conducted and a tissue-conducted injury In general, an air-conducted injury affects the anterior segment of the eyes, and a tissue-conducted injury, the posterior section of the eye Of course, there are exceptions, but in general this relation emerges from their material In listening to the paper this afternoon, I got the impression that the same factor was present in this material

DR S RODMAN IRVINE, Beverly Hills, Calif. The value of the contributions Dr Rones and Mrs Wilder have made to knowledge of ocular pathology resulting from contusion injuries lies particularly in their analysis of the condition of the eyes with respect to the interval of time following injury An experimental study on animals was made by Dr George Kilgore, who produced varying degrees of contusion injury in monkeys and made an extensive study of the pathologic changes at various times after injury (Kilgore, G *Am J Ophth* 25: 1095-1099 [Sept] 1942) The present authors have made a some-

what similar study on the human eye, taking advantage of the large series of eyes removed after injury, available at the Army Institute of Pathology

One is impressed by the extensive damage that may occur to the eye as a result of a concussion or contusion injury, this, I believe, is not generally appreciated. Clinically, there is no doubt that one is often deceived by the appearance of an eye immediately after such an injury. It is only when recurrent hemorrhages take place and secondary glaucoma develops that the clinician is aware that a major disaster has occurred.

I wonder whether the authors encountered anything in particular that would lead them to predict that an eye would have recurrent hemorrhages, how soon blood staining of the cornea might occur if blood were allowed to remain in the anterior chamber in a glaucomatous eye and how soon cupping of the disk might be expected. Dr. Rones mentioned that in 1 case cupping occurred about six weeks after injury, but I wonder whether there are other cases in which the time interval might have been more definite. These are important questions to the clinician who desires to know how much leeway he has before it is necessary to evacuate the anterior chamber and remove the blood.

It is interesting to me that there was no incidence of sympathetic ophthalmia in spite of there being tremendous disorganization of the ciliary body and pigment throughout the globe. This confirms the observation that a perforating injury is necessary for sympathetic ophthalmia to develop, and it strengthens the theory of infection through the portal of perforation and detracts from the theory of sensitization to one's own pigment as a cause of sympathetic ophthalmia. I am aware that sympathetic ophthalmia without perforation, particularly in cases of tumor, has been reported, but it is so rare that the burden of proof is on those who report such cases.

Since many of the eyes showed detached retina and extensive hemorrhage in the posterior segment, I wonder whether the authors can venture an explanation as to why the incidence of fibrovascular membrane on the iris is so low. I believe it was mentioned in only 1 case.

I wonder whether Dr. Rones would care to say anything about the incidence of the Vossius ring, which Dr. Trygve Gundersen described so well as following contusion injuries in young people, and which does not occur in elderly persons. It is a pigmentary disturbance, with a diameter a little smaller than that of the pupil, and probably lies under the epithelium of the lens, it seems that this series would afford a wonderful opportunity to study the condition.

Regarding case 18, one of gunpowder injury, showing a rather extensive inflammatory response in the eye, I wonder whether this reaction could be explained on the basis of injury to the cornea. Studying the aqueous in rabbits, I found the response in cells and protein in the aqueous conspicuous after inflammation localized in the center of the cornea. For example, I found that it produced a much greater response, as indicated by cells and protein in the aqueous, than trauma of the same severity in the periphery of the cornea. If the cornea in this case had been extensively damaged by gunpowder, I should

expect an intense inflammatory response in the interior of the eye. No mention of the condition of the anterior surface of the cornea was made.

Finally, after reading this paper, one considers what benefit the physician called on to treat such injuries can derive from the pathologic studies Dr Rones and Mrs Wilder have presented.

Since hemorrhage and secondary glaucoma are the immediate complications, treatment should be directed against them. Such treatment might include complete immobilization of the eyes by snug double eye bandages, rest in bed, use of ice compresses, instillation of miotics and early surgical intervention for removal of blood. It would seem that wide incision and frequent irrigations of the anterior chamber, and possibly corneoscleral trephining, are necessary to accomplish this. The question of advisability of removal of a dislocated lens is to be considered. The use of calcium, a vitamin K preparation or any other means of inhibiting bleeding would seem important.

I wish to congratulate Dr Rones and Mrs Wilder on their present study of the material at the Army Institute of Pathology. We all await the results of their further analysis of the abundant material available to them.

DR BENJAMIN RONES, Washington, D C. We are deeply grateful to Professor Riddell and Dr Irvine for their discussions of this paper. It is rather formidable to have thrown into your lap a paper of this scope. The reading of it was much simpler than the task the discussers had in wading through forty-seven detailed protocols and summaries of all the other material. We appreciate their attempt to make clinical sense out of this paper.

We also appreciate the audience's attention in the presentation of this material.

With regard to Professor Riddell's discussion, I again wish to emphasize that there were no cases in this series of penetrating injuries of the eye. The wounds are all nonpenetrating, consequently, no eyes in this series contained glass, metal or inorganic substances. There are many other eyes at the Army Institute of Pathology with penetrating wounds, and they will be classified and studied at some later date.

I am pleased with Professor Riddell's suggestion of the time limitation. However, he must bear in mind that a considerable number of these eyes were removed at field stations and hospitals where the operating surgeons were under great pressure. There was no follow-up study of the patients. After considerable difficulty, we arrived at the time-spacing relation on the basis of information that was as accurate as we could get, but not so detailed as a day to day notation would signify.

The value of this material lies in the fact that one has an almost experimental set of circumstances. If one is working with animals, one produces an injury, removes the eye in one, two or three days, or after any length of time desired, and then studies the damage and reparative processes that are present. For the first time we have this set of circumstances in a large series of human eyes, and I think therein is the chief value of this material.

Dr Irvine asks How can one tell when an eye will have recurrent hemorrhages? Pathologically, one can say that granulation tissue is composed of fresh young blood vessels, consequently, such capillary buds are likely, under many conditions of strain and stress, to give way and produce another hemorrhage in the eye How soon blood staining of the cornea may occur it is difficult to say, because that depends a great deal on the tension of the eye and on how many pigment granules are forced to migrate into the corneal stroma

With regard to the cases of early glaucoma, the earliest occurrence we had in this series was six weeks after injury There are a number of cases of other types of injury in which cupping occurred considerably earlier

With regard to the fibrovascular membranes, we mentioned their occurrence in 5 cases, and in many others in which they were not mentioned, organizing masses of hemorrhage in the anterior chamber and inflammatory exudates in the pupillary region and over the iris were observed

### **Anatomic Variations in Attachment of the Oblique Muscles of the Eyeball** DR WALTER H FINK, Minneapolis

An anatomic study was made of the superior and inferior oblique muscles The problem was confined to the insertion of these muscles and their relationship to the adjacent rectus muscles The work was approached from the clinical standpoint, and with the hope that, with a broader knowledge of the anatomic relations of these muscles, ability of ophthalmologists to diagnose and treat the obscure muscular defects would be increased

Although the series of specimens was small and the data were restricted to the insertion of these muscles, certain conclusions were reached

1 The anatomic variations in the insertion of the superior oblique muscle are more numerous than those of any other extraocular muscle Variations in the insertion of the inferior oblique muscle are next in frequency

2 The wide variation in the position of insertion of these muscles suggests the possibility that a "paretic" muscle may be abnormal in action because of an unusual insertion It is likely that many of the obscure defects in the action of these muscles may be explained by a variation in the insertion into the eyeball

3 The work indicates that a favorable and feasible surgical approach could be made at the insertion of the superior oblique muscle

4 The study suggests the possibility of a more satisfactory surgical management of paralyzes of the inferior oblique Surgical intervention can, and should, be directed to the insertion rather than to the origin because of the easier approach to and the anatomic relations of the former

5 The possible intimate relation of the inferior oblique muscle to the optic nerve and other important structures should be kept in mind in operations on the muscle

Extraocular muscle surgery would take a step forward if a more accurate technic could be applied to procedures on the oblique muscles

As matters stand now, possibilities for correction of a defect of an oblique muscle are limited. This state of affairs is due apparently to lack of knowledge concerning the anatomy of the oblique muscles.

It is surprising how few data are available concerning the variations in these muscles. The inquiring student is faced only with generalities. If the need for more exact data on this subject could be appreciated, more work would be forthcoming, and greater possibilities for scientific work on these obscure and poorly understood muscles would be opened.

#### DISCUSSION

DR F BRUCE FRALICK, Ann Arbor, Mich. Dr Fink has started on a commendable research project, which, when completed, will add materially to general knowledge of the anatomy of the extraocular muscles. The statistical analysis of the results of the investigation can be fully appreciated only after careful study of his beautiful display in the scientific exhibit. Only then is one able to comprehend the thorough and painstaking work needed to supply the information which he has given us today.

A fearful approach to muscle surgery is engendered by uncertainty regarding the diagnosis, physiology or anatomy of the extraocular muscles. Acquisition of knowledge of the anatomic relations presented by Dr Fink will lead to better operations on these muscles than are now generally done.

The various measurements of the ocular muscles need not all be remembered, since not every one is of great clinical value. Some of the measurements given aid the ophthalmic surgeon in locating the muscles at operation. For instance, if the surgeon did not know that the global insertion of the inferior oblique muscle was about 10 mm posterior to the insertion of the external rectus muscle, difficulty might be experienced in finding the insertion when recession or resection of this muscle is attempted. If it is remembered that the anterior edge of the superior oblique tendon is only about 2.5 mm behind the nasal edge of the insertion of the superior rectus muscle, no trouble should be experienced in finding this tendon for resection or recession. Not all these data are available in any standard text of ophthalmology or ophthalmic anatomy.

For many years my colleagues and I have been teaching our residents the necessity of retaining normal anatomic relationships of the extraocular muscles when performing operations on these muscles. The surgeon should have great respect for the fibrous sheath of the muscle and leave it intact. Stripping of the sheath from the muscle and tendon leads to adhesions of the muscle to the sclera.

Dr Fink has emphasized that in performing recessions not only should the tendon be spread out to the normal breadth of insertion present in the particular eye, but the recession should be measured equally from the two ends of the scleral insertion. The only exception to this rule is in those rare eyes in which the line of insertion is definitely abnormal. A muscle cannot be reattached to the globe with a single central suture with the expectation that that attachment will have a spread of approximately 10 mm. Very likely a narrow point of

attachment would have little effect on the efficiency of the lateral and medial rectus muscles when the eye is moved in the horizontal plane

This narrow point of insertion could conceivably have a serious effect on the efficiency of these muscles when they are used in the oblique or the vertical position of gaze

I can see no excuse for the rather common practice of reinserting a medial or a lateral rectus muscle higher or lower in an attempt to correct a hyperphoria or hypertropia. Such a practice is an admission of inadequate diagnosis of the anomaly at hand

I agree with Dr Fink on the advisability of spreading the scleral insertions of the oblique muscles to their normal width when recession or resection is done. This principle should apply as much to the oblique muscles as to the rectus muscles. It is far more difficult to reattach the oblique muscles than the rectus muscles, and considerably more manual dexterity is required to insert two sutures in order to obtain the normal width of the attachment. This is especially true when recession of the inferior oblique alone is performed, without resection of the external rectus. More exposure is afforded when recession of the inferior oblique is combined with resection of the lateral rectus, but even then I have found difficulty in placing the posterior suture far enough back on the globe

My poorest results from recession of the inferior oblique have been due to incomplete severance of the scleral attachment posteriorly. Since this attachment extends within 5 mm of the optic nerve, one is working blindly with scissors in making this section. It is, therefore, not difficult to leave some of the posterior fibers intact

I cannot agree with Dr Fink's interpretation of the line of action of the inferior oblique and his method of suturing the inferior oblique to the sclera along this line. If he reattaches the anterior end of the tendon at the same distance from the cornea as it was originally he is placing the new insertion too far posteriorly and his new line of action will be more oblique than formerly. It is my belief that the new insertion should be along the normal line of action of the muscle. This line of action extends obliquely forward and down around the globe

Dr Fink has pointed out the relation of the superior rectus to the superior oblique. I feel that an even more important relationship is that of the superior rectus and the levator oculi muscle. The union of the superior rectus and the levator muscle is so strong that if the amount of recession of the superior rectus is too great the upper lid will be elevated, giving an apparent exophthalmos on this side. On the other hand, if the superior rectus is resected too much, relative ptosis will result. The same relationships are present in the lower lid, although here there is no levator tendon. Fascial bands passing from the inferior rectus to the lower tarsus act in the same manner as the levator muscle of the upper lid. Too generous recession of the inferior rectus widens the palpebral fissure as a result of the lower lid being pulled down. Too extensive resection of the inferior rectus causes elevation of the lower lid, with resultant narrowing of the palpebral fissure

DR RAYNOLD N BERKE, Hackensack, N J. Dr Fink's presentation is timely and to the point. It is timely because never before have so many operations been proposed for the treatment of hypertropia

associated with overaction or underaction of the oblique muscles. These operations may be briefly noted as follows:

(a) To decrease the action of the inferior oblique muscle, Dr J H Dunnington, a number of years ago, advocated myectomy, tenotomy or myotomy of the overactive muscle. Later, Dr J W White described an operation for recession of the inferior oblique muscle to decrease its action.

(b) To increase the action of the inferior oblique muscle, Dr J M Wheeler designed an operation for advancing the tendon of this muscle over the lower margin of the orbit. Later, Dr J W White suggested tucking the inferior oblique muscle to increase its action.

(c) To increase the lifting power of the superior oblique muscle, Dr Wheeler, a number of years ago, designed an operation for tucking the reflected tendon of this muscle. Recently, Dr J M McGuire gave a description of an operation, which I understand is now in print, for resecting the tendon of the superior oblique muscle to increase its action.

(d) To decrease the action of the superior oblique muscle, Dr W L Hughes advocated recession of its pulley. Dr Fink suggested that it may be feasible to tenotomize the superior oblique muscle lateral to or under the superior rectus muscle. Three months ago I described an operation for tenotomy of the superior oblique on the nasal side of the superior rectus.

Thus, a total of eight operations are available for the treatment of hypertropia associated with dysfunction of one or more oblique muscles.

Surgeons who perform these operations frequently say that they are easy and simple to do. Surgeons who do them rarely, or not at all, believe that they are difficult. This difference of opinion, I believe, is due to familiarity with the anatomy of those who do the operations frequently.

Dr Fink's paper brings up a number of interesting and practical points. I should like to enlarge briefly on two or three of them. He has shown that the insertion of the inferior oblique muscle begins about 10 mm posterior to the inferior edge of the insertion of the external rectus muscle and from this point recedes backward in the average case for a distance of about 10 mm. The entire insertion of the inferior oblique usually lies under the inferior half of the belly of the external rectus. Obviously in doing a recession of the inferior oblique muscle, it is necessary to keep this relationship in mind. One should also remember this relation in every operation on the external rectus, for it is possible accidentally to tenotomize this muscle during a resection, recession, tucking or advancement of the muscle. I know of such an accident, in which the inferior oblique muscle was accidentally tenotomized during a routine resection of the external rectus muscle [drawing explaining how accident may develop]. After the conjunctiva has been incised and an opening made in Tenon's capsule, the muscle hook is passed under the external rectus muscle, and during this maneuver the belly of the inferior oblique may be accidentally picked up, because the insertion is farther forward than normal, because the hook is passed too deep into Tenon's space or, for some other reason, the inferior oblique muscle is brought forward to a position directly under the insertion of the external rectus muscle. One can readily see how easy it would be for the surgeon, when freeing the external



rectus muscle from Tenon's capsule, to sever accidentally the inferior oblique muscle. In the case to which I referred, a second operation was done, at which time the inferior oblique was observed to be attached to the sclera at the insertion of the external rectus muscle, having been completely severed from its normal attachment. It is necessary only to keep this possibility in mind in operations on the external rectus muscle to avoid this complication.

Dr Fink has shown that the reflected tendon of the superior oblique muscle passes only 2 or 3 mm posterior to the insertion of the superior rectus muscle. This is important, as already brought out by him and Dr Fralick, because in doing an operation on the superior rectus muscle the tendon of the superior oblique muscle may accidentally be severed. I know of one such accident.

Dr Fink has suggested that it may be possible to tenotomize the superior oblique muscle lateral to the superior rectus muscle. In this he is correct, but, unfortunately, tenotomy of the superior oblique muscle at this place is difficult and uncertain. It is difficult because the insertion of this muscle extends so far posterior to the equator. It is uncertain in its effect because one cannot be sure that all the fibers have been severed from the globe. Unless they are all severed, little or no effect will result. Of 4 tenotomies of the superior oblique done lateral to the superior rectus at the Institute of Ophthalmology of the Presbyterian Hospital, only 1 was entirely successful. In the 3 unsuccessful operations, the failure was attributed to incomplete tenotomy.

A better site of tenotomy of the superior oblique muscle is on the nasal side of the superior rectus muscle. This is the site of choice, for the following reasons:

First, the reflected tendon of the superior oblique muscle at this point is well forward, being only 2 or 3 mm from the insertion of the superior rectus muscle.

Second, the width of the tendon of the superior oblique muscle at this point is only 5 or 6 mm, the tendon being compact. These two features make it easy to pick up the reflected tendon of the superior oblique muscle.

Third, if the operation is done at this point, it is not necessary to remove the superior rectus or to disturb its insertion, as would be the case if the operation were done lateral to the superior rectus muscle.

Fourth, there are at this point no important nerves, arteries, veins or other periocular structures which might accidentally be injured during the operation.

Finally, if the operation is done here, it will be done under Tenon's capsule and within the sheath of the superior oblique muscle. If the operation is done here, complete paralysis of the superior oblique muscle will not follow the operation.

DR WALTER H FINK, Minneapolis. In answer to the question of interpretation of the anatomic variations. I cannot with certainty diagnose a case of abnormal insertion. There is the possibility that in a certain percentage of cases the abnormal muscular action is due to an abnormal insertion.

I believe that tenotomy of the superior oblique should be done on the tendon, and not on the insertion. I think that Dr Berke is correct, and I am in full agreement with his approach, for to me it is the most logical procedure.

## NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Brittain F. Payne, M.D., *Chairman*Milton L. Berliner, M.D., *Secretary**April 21, 1947*

## INSTRUCTION HOUR

Fitting of Glasses for Aphakic Eyes. DR. DANIEL B. KIRBY

Condition of the Eye After Cataract Extraction. DR. DANIEL B. KIRBY

## PAPERS OF THE EVENING

New-Formed Vessels in the Fundus Oculi PROF. A. J. BALLANTYNE  
(by invitation), Glasgow, Scotland

The terms "new-formed" and "new-built" as applied to certain vascular anomalies of the fundi are not strictly accurate but are convenient expressions to describe vessels which make their appearance under pathologic conditions in the vascular tissues of the fundus or grow from such tissues into a normally avascular neighborhood. They vary greatly in form and may be intraretinal, subretinal or preretinal. They can be studied with the ophthalmoscope in the living eye, with the loupe or the binocular microscope in the excised eye and with higher magnification under the microscope, in bulk or in sections. Nothing quite analogous is known in general pathology. Such vessels may exist but are not recognizable in the course of ordinary histologic examination.

The most familiar forms of new vessels are seen in the networks of venules spread out within, or on the anterior surface of, the retina, the so-called rete mirabile, and, often associated with these are tufts, or glomerular formations, of fine veins projecting into the vitreous, embedded in an almost invisible supporting tissue. Most, if not all, of these intraretinal networks can be formed by the expansion of pre-existing venules and capillaries. They are usually encountered in cases of obstruction of retinal veins and provide a collateral circuit to accommodate the venous blood stream.

The preretinal vessels and vitreous tufts occur in similar circumstances and may have a similar function, but their purpose is not understood. It has been suggested that the vitreous tufts perform the function of removing retinal exudates and hemorrhages. The preretinal vessels are correctly described as newly formed, they originate from the retinal veins by budding. They are able to penetrate the internal limiting membrane and are not necessarily preceded by retinal hemorrhage.

Varicose vessels on the optic disk also occur when there is venous obstruction, usually thrombosis of the central retinal vein or one of its branches. They also provide a by-pass for the venous circulation. They may be formed by the expansion of preexistent vessels on the disk. Artery-to-vein and artery-to-artery anastomosis are also, but less frequently, observed in the retina, and an unusual form is anastomosis of a retinal vein with the choroidal vascular system through a small choroidal coloboma.

The vessels which originate in the choroid, perforate the membrane of Bruch and spread between the choroid and the retina as a vascular membrane (Reichling and Klemens) are seen ophthalmoscopically in association with senile central exudative and hemorrhagic retinitis and may be described as one of the forms of angioid streaks. These vessels, like the preretinal networks, may have the function of carrying off the harmful products of local disease.

Histologically, most of the new-formed vessels have the appearance of greatly enlarged capillaries, but there is a type of much larger new-formed veins, seen chiefly in diabetes, with walls of varying thickness, which present the characters of phlebitis, phlebosclerosis and hyaline and fatty degeneration.

An interesting type of new-formed vessels, which so far has been identified only histologically, has been described by Prof. A. Loewenstein (1946) as intramural vessels. They occur in cases of vascular disease, are situated within the walls of the vessels, communicate here and there with the lumen of the parent vessel and sometimes form an elongated network in the vascular wall.

The line of demarcation of these vessels from the vessels which canalize a venous thrombus, or which appear in the optic nerve as collaterals of the obstructed vein, has not been determined. They have certain points of resemblance to the intramural vessels described by Winternitz and associates (*The Biology of Arteriosclerosis*, Springfield, Ill., Charles C. Thomas, Publisher, 1938) as occurring in the aorta, the renal arteries and other large vessels.

#### DISCUSSION

DR. BERNARD SAMUELS: I am not prepared to discuss Professor Ballantyne's fine presentation, but I should like to ask him for the anatomic reasons which brought about the secondary glaucoma and loss of the eye in his case. In some cases of occlusion of the central vein glaucoma develops and necessitates the loss of the eyeball, whereas in others the condition goes on for years and glaucoma does not develop.

PROF. A. J. BALLANTYNE, Glasgow, Scotland: I am sorry that I cannot throw light on this unsolved problem. I have no personal knowledge of that point, and I should not like to speculate on it.

DR. ARNOLD KNAPP: It is a great privilege to hear Professor Ballantyne speak on a subject to which he has made such important contributions—a subject which is fascinating and, at the same time, very difficult. I am particularly impressed by his demonstration of the formation of new vessels on the head of the optic nerve and of the development of new vessels which, after they break through the inner layer of the retina, spread out under the hyaloid membrane. I should like to have him give us his interpretation of the reasons for the tremendous development of new vessels in cases of what is regarded as malignant diabetic retinitis.

PROF. A. J. BALLANTYNE, Glasgow, Scotland: My interest in these new-formed vessels really began in the study of diabetes. In cases of diabetic retinopathy these gross changes appeared in the retinal vessels, and it was only in cases of diabetes that Dr. Loewenstein and I were able to demonstrate the perforation of the retina. There was only 1 exception to this in the material which we examined, the case being

the one first illustrated on the screen, with a peculiar plexus in the course of the superior temporal vein. The case was one of hypertension without glycosuria. The state of the blood sugar was not recorded. The sections showed well the vein breaking through the anterior layer of the retina and forming a plexus which spread over the surface. I cannot help feeling, in spite of that exception, that there is a specific connection between diabetes and these gross changes in the retinal vessels. Comparison of a case of diabetic retinopathy and one of hypertension with vascular changes in the retina shows a difference in the history of the retinopathy, as well as in the ultimate changes in the retina, in the two conditions. In the case of diabetes, there is no discoverable connection between the disability or the age of the patient, or many other factors, and the presence or severity of the retinopathy. A patient with diabetes may never show more than fulness of the retinal veins. Again, a patient may show nothing more than minute capillary networks and aneurysms in the retina, and these may remain unchanged for years. We have had 1 or 2 patients under observation for four or five years without alteration in these lesions. Then, a sudden change for the worse may occur in the course of the diabetic retinopathy, with the appearance of gross vascular lesions, hemorrhages, exudates and changes which destroy the eye, even though the patient is comfortable and the diabetes is well controlled. In cases of hypertension the first sign is the presence of minute hemorrhages radiating from the disk. At the same time woolly patches and other exudates appear. Sooner or later retinal changes not found with diabetes occur, chiefly the result of arteriosclerosis, and it is only at a late stage that evidence of thrombosis of the retinal vein is observed and a network of new-formed vessels is seen. Another fact of importance is that by the time the hypertensive patient has manifested advanced changes of this kind his expectation of life is short. Except for persons with venous thrombosis and secondary glaucoma, one does not often see a patient with hypertension living for years with blindness due to retinopathy. But in the case of diabetes a comparatively young patient may lead a reasonably healthy life but be blind, owing to the presence of exudates and hemorrhages. These two conditions are in distinct contrast, and it is our feeling that the combination of hypertension and diabetes does not have much to do with it, but that there is something specifically different in the two conditions which makes them develop along different lines. At least 50 per cent of our patients with diabetic retinopathy do not have hypertension.

DR JOSEPH IGRSHEIMER. Professor Ballantyne has demonstrated an interesting case of thrombosis of the central vein without retinal hemorrhages. I should like to ask whether the diagnosis in this case was made clinically, or only microscopically, and, second, whether the glaucoma, as usual, followed the thrombosis, or whether it came first and the thrombosis later?

PROF A. J. BALLANTYNE, Glasgow, Scotland. For several years the case was diagnosed as one of thrombosis on the basis of the appearance of the retinal veins and those on the disk. The condition was anomalous in the absence of hemorrhage. I cannot tell at what stage the diagnosis of glaucoma was made.

**Medical Needs of the Philippine Islands** DR HERMENIO VELARDE  
(by invitation), Manila, Philippines

Dr Velarde spoke interestingly on the conditions during the siege of Manila and of the plight of ophthalmology, as well as of medicine in general, in the Philippines during the reconstruction

DISCUSSION

DR BRITAIN FORD PAYNE My first visit to one of the war-wrecked medical centers of the Philippine Islands was early in May 1945 All that remained standing and serviceable was a portion of the Philippine General Hospital, which is about a mile from the city wall of Manila

All that was left of the recently completed clinic and laboratory buildings was charred walls and mangled equipment Live "booby traps" or bombs were concealed in the rubbish and ashes The administration building of the hospital was so damaged by shells and bombs that it was abandoned A strafed ambulance stood in front of the building as a reminder of the ferocious battle for Manila two months before

Other buildings were so damaged by the retreating Japanese that they will have to be rebuilt from the ground up The medical school, the cancer institute, the school of nursing and the postgraduate school, all modern and well equipped buildings, were completely gutted and wrecked

With so much of the physical plant ruined by battle, and so much suffering from wounds, starvation and death, the civilian doctors and nurses of the staff stood by to render what aid they could The civilian doctors worked night and day with the sick and wounded, native and American alike, not knowing whether the next shell or bomb would strike them The day after the Japanese were pushed into the walled city, the hospital was operating with every available cot or bed taken by sick or wounded Many single beds were occupied by mother and child, both sick or wounded, and some were lying on the bare floor

An inspection of the main hospital showed that some additional space was available, though there were craters in the floor and roof and parts of the walls were gone Immediate repairs were made, and hundreds of patients were given shelter Practically all laboratory equipment was gone, x-ray machines were destroyed, and the library was burned to the ground Only three microscopes could be salvaged for the entire center, and these had been hidden away in the early days of the Japanese occupation

It is difficult for us to visualize the hopelessness of the situation as it was in Manila during the Japanese occupation and while liberation was in progress Most of the doctors in this country would find it difficult to work with bare hands, no drugs and little or no equipment The Filipino doctors found it difficult also, but they had had some experience under Japanese domination, and they are doing their best today with the little they have The American doctors, for example, Musgrave, Strong and Heiser, would be proud, if they knew, of the excellent record made by the great medical center they founded and the physicians they trained

The University of the Philippines was founded at the turn of the century by Americans, and the medical center was a major part of the

university The other great center and medical school in Manila was a part of the University of Santo Tomas It was used by the Japanese as a crowded prison camp and by the American Army as a military hospital after the liberation It will be reopened for classes as soon as its war damage is repaired and new buildings can be constructed Both these fine institutions need immediate aid in the form of books, instruments, drugs and magazines The libraries have been pilfered and burned, and hundreds of Filipino doctors have not seen a copy of *The Journal of the American Medical Association* since December 1941 This is true of other journals and books All reference copies have been lost, and old, as well as new, journals are needed for teaching and investigation Instruments for surgery and clinical investigation are badly needed American ophthalmologists have been most liberal in furnishing instruments, but the need extends to equipment for general surgery and medicines as well

Equipment for the study and drugs for the treatment of tropical diseases should be sent to Manila as soon as possible It has been wisely said by Dr Velarde that our progress in treatment of tropical diseases in this country will be advanced in proportion to our interest in research in the Philippine Islands

The program of research on tropical diseases would be stimulated by our sending literature and material for investigation Many Filipino physicians come to our great medical centers for training, and many of them are graduates of our medical schools The dean of the medical school, Dr. A G Sison, is an alumnus of the University of Pennsylvania and has kept standards well within the requirements of the Association of American Medical Colleges The Philippine Medical Association is similar to the American Medical Association Interchange of students and research workers should be encouraged in order that we may understand tropical disease and treat many of our veterans so afflicted

We Americans should never forget the aid the Filipinos gave us while so many of our citizens were imprisoned by the Japanese We should never forget the aid loyal Filipinos gave MacArthur's army, and we should help them in reestablishing themselves medically and economically They do not need money as such, but they do need books, instruments and drugs

#### **An Integrated Artificial Eye and "Vitalium" Implant for Use in Enucleation and Evisceration. DR WENDELL L HUGHES, Hempstead, N Y.**

Three types of implants have been designed, all in "vitalium," each of them to be integrated with the same type of artificial eye so that the motion of the implant is imparted to the eye and the eye is held up to support the upper lid in a normal manner

All the implants have the same type of face, which is left exposed in the socket, with an oval depression anteriorly The eye is designed with an oval peg on its posterior (concave) surface to fit into this depression

1 *Enucleation Implant*—The first type, for use at the time of enucleation, has a circular attachment bar, to which the rectus muscles

are attached in the horizontal and vertical positions and the fascia bulbi is attached in the quadrants of the four oblique muscles

2 *Replacement Implant* —The second type has a smaller body posteriorly and is designed to replace the usual type of buried implant now in use. This implant has a similar ring for the attachment of the muscles and fascia

3 *Evisceration Implant* —The third type, designed for use at the time of evisceration, has a similar anterior face and fits inside the sclera. The evisceration is performed and the implant is inserted through an incision posterior to the insertion of one of the rectus muscles. The muscle tendon is first detached and is replaced later onto the anterior lip of the scleral wound to aid in holding it together. The cornea is removed to allow the anterior surface of the implant to protrude through. Movement of the eye is better than with the conventional type of implant because the motion of the implant is transferred to the eye by means of the integrating depression on the implant and the peg on the posterior surface of the eye. In the old, buried, type of implant there must of necessity be considerable lost motion or slippage between the implant and the eye.

The upper lid is supported because the eye is held up by its direct connection with the implant, eliminating the depression usually present with the conventional type of artificial eye, the entire weight of which must rest entirely on the lower lid.

Kodachrome slides and moving pictures illustrated the details of design and technical procedure in use of the replacement implant.

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## AMERICAN OPHTHALMOLOGY DURING THE PAST CENTURY

F H VERHOEFF, M D  
BOSTON

Acceptance of the invitation to be your guest at this memorable meeting of the American Medical Association imposed on me the duty of addressing you on the subject of the history of american ophthalmology. In view of this terrifying obligation, my presence here attests my profound appreciation of the honor you have conferred on me. The address to which I have given birth after much labor, I fear is but a mouse. Although largely about ophthalmologists of the past, it is not an obituary, for in it I try to speak the truth, the whole truth and nothing but the truth. To relieve any anxiety this statement may arouse, I hasten to add that no ophthalmologist now in active practice is mentioned by name.

One hundred years ago there were, strictly speaking, no ophthalmologists. However, there were a few doctors here and there who devoted an unusually large part of their practice to diseases of the eye and hence may be called part time ophthalmologists. It is not clear whether they became such by their own choice or by choice of the public. As to the mother of american ophthalmology, histories are silent, but Elisha North (1771-1843), of New London, Conn., Philip Syng Physick (1768-1837), of Philadelphia, and George Frick (1793-1870), of Baltimore, each has been designated the father. In 1847 only one of these alleged parents was alive, and he had retired from practice. Of the part time ophthalmologists who were then in active practice the most notable were, in Philadelphia, William Gibson (1788-1868), Isaac Hays (1796-1879), William E. Hoener (1793-1853) and Squier Littell (1803-1880), in Louisville, Ky., Samuel D. Gross (1805-1884), in Baltimore, Nathan R. Smith (1797-1877), in Boston, Edward Reynolds (1793-1881), John Jeffries (1796-1876) and John H. Dix (1813-1884), in New York, Edward Delafield (1795-1875), William Clay Wallace and Alfred C. Post (1806-1886).

To American doctors of 1847, two American textbooks on diseases of the eye were available, one (1823) by George Frick<sup>1</sup> and the other

Read before the Section on Ophthalmology, at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, June 12, 1947



(1837) by Squier Littrell<sup>2</sup> These were largely based on Beer's German textbook<sup>3</sup> of 1817 Also available were several British textbooks, the best of which was the "Practical Treatise on Disease of the Eye" (1830)<sup>4</sup> by William Mackenzie of Glasgow, Scotland The gross structure of the eye was relatively well known, and something was even known as to the histology of the eye James Wardrop, of Scotland, later of London, in 1808 had classified and named diseases of the eye according to the structures chiefly involved Thus, he was the first to use the term keratitis What was known in 1847 concerning diseases of the eye is revealed by perusal of the textbooks mentioned The chief topics in Littell's textbook were diseases of the orbit, including tumors, and aneurysm by anastomosis (for which ligation of the carotid artery was advised), diseases of the lacrymal organs, inflammation of the eyelids, syphilitic infections of the eyelids, tumors of the eyelids, hordeolum, ankyloblepharon, symblepharon, ectropion, entropion, trichiasis, distichiasis, lagophthalmos, ptosis, conjunctivitis, "varolus ophthalmicus," pterygium, xerosis, acute corneitis, pannus, abscess of the cornea, ulcer of the cornea, staphyloma of the cornea, conical cornea, scleritis, choroiditis, retinitis, iritis, cataract, hydrophthalmos, glaucoma, cancer of the eye, melanosis (malignant melanoma), fungus hematoïdes (retinoblastoma), paralysis of muscles of the eye, day blindness, night blindness, amaurosis, muscae volitantes, strabismus, myopia and presbyopia It is interesting, that although thirty-two years were to elapse before the discovery of the gonococcus, it was known that purulent conjunctivitis was sometimes caused by gonorrheal infection A form of keratitis due to hereditary syphilis had not been recognized, for Hutchinson had not yet made his great contributions to ophthalmology The term amaurosis was used to hide ignorance of many conditions with which one is now familiar Retinitis and choroiditis were known to occur, but in actual cases their existence could only be guessed at, for the ophthalmoscope had not yet been developed<sup>5</sup>

Perimetry had not come into being, and refraction tests were not made—no doctor possessed a trial case of lenses Glasses were not pre-

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1 Frick, G A Treatise on the Diseases of the Eye, Including the Doctrines and Practice of the Most Eminent Modern Surgeons, and Particularly Those of Professor Beer, Baltimore, F Lucas, Jr, 1823

2 Littell, S, Jr A Manual of the Diseases of the Eye, Philadelphia, J S Littell, 1837

3 Beer, G J Lehre von den Augenkrankheiten, als Leitfaden zu seinen öffentlichen Vorlesungen entworfen, Vienna, Camesina, Huebner u Volke, 1813-1817

4 Mackenzie, W A Practical Treatise on the Diseases of the Eye, London, Longman, [and others] 1830

5 It is interesting to note that 1847 was the year that Bakkage demonstrated his model of the ophthalmoscope to the English ophthalmologist Wharton Jones, who rejected it It was not until four years later that von Helmholtz, independently, invented another model and established its significance

scribed by physicians but were fitted at the discretion of opticians. Cylindric lenses were not yet available. Ether anesthesia was just coming into general use, but local anesthesia was unknown. Operations were done on the lids for entropion, ectropion, and the like, but the only important operations on the eyeball itself were discussion of cataract, extraction of cataract, making of an artificial pupil and enucleation. Paracentesis for glaucoma was sometimes done, but the value of iridectomy for this condition was still unknown.

Atropine was used to combat iritis, but the antiglaucomatous effects of physostigmine and pilocarpine had not yet been discovered. Some of the drugs employed in collyriums, ointments or powders may be noted: mercury in several forms, including mercury bichloride, silver nitrate, zinc sulfate, zinc oxide, copper sulfate, lead subacetate, tincture of iodine, sodium borate, camphor, and opium. Strychnine, quinine, oil of turpentine, preparations of iron, and tincture of colchicum seed were among the drugs given by mouth. Cathartics were regarded as highly important in the treatment of many conditions. Venesection was freely employed for almost all serious ocular conditions, including iritis. Setons, blistering agents and leeches were also frequently employed. I can recall that as late as 1900 leeches were kept on hand at the Massachusetts Eye and Ear Infirmary and were frequently used by the older surgeons. They were usually applied to the temple and were believed to allay pain and assist in dilatation of the pupil in cases of iritis. Their use has died out without being openly condemned by any one. Since leeches add something to the blood which hinders its coagulation, possibly they did have beneficial effect on certain inflammatory conditions. Littell stated that it was often impossible to distinguish syphilitic from diopathic iritis, but that this was unimportant, since the same treatment was used for the two diseases.

From what I have said, it is obvious that in 1847 ophthalmology was in a highly primitive state. This was especially so in America, for here medical education in general was woefully inadequate. In those days, and for many years afterward, specialism was frowned on by the medical profession. Even in 1864, when the American Ophthalmological Society was founded, many of its members, including its first president, Edward Delafield, practiced general medicine or surgery along with ophthalmology. Moreover, from 1868 until within recent years this society had a rigid rule excluding from membership any one who in any public way designated himself a specialist. Its purpose was to prevent the public from assuming that oculists were not physicians. Only a few years ago, for the same reason, the term "eye physician" was suggested as a substitute for ophthalmologist or oculist.

However, in spite of the lack of real specialists in 1847 three special hospitals had already been founded and were in active operation, namely, the New York Eye Infirmary (1820), the Massachusetts Charitable Eye

and Ear Infirmary (1824) and the Wills Eye Hospital (1834) These hospitals were founded because of the meager facilities provided for the specialties in general hospitals Such complete isolation of the specialties has proved to be unwise, for this reason the Massachusetts eye and Ear Infirmary, originally a completely independent institution, has become closely affiliated with the adjacent Massachusetts General Hospital

The first American to restrict his practice exclusively to ophthalmology was Henry W Williams (1821-1895) He did this in Boston a few years after his graduation from Harvard Medical School He entered this school in 1844, but after two years went to Europe, where for three years he studied ophthalmology in addition to general medicine He then returned to Harvard and obtained his medical degree in 1849 Throughout the greater part of his active life he remained the foremost American ophthalmologist of his day, and in 1871 he became the first professor of ophthalmology at the Harvard Medical School On his retirement, in 1891, he endowed the professorship, which was then given his name This, however, was not the first chair of ophthalmology to be established in this country, for in 1860 Miami Medical College had created such a chair for an almost equally eminent specialist, Elkanah Williams (1822-1888), of Cincinnati, who is also given credit for being the first to restrict his practice to diseases of the eye, ear, nose and throat These men were not brothers, as sometimes has been assumed, or, so far as is known, even distantly related In 1862 Henry Williams published an ophthalmologic textbook<sup>6</sup>, which passed through several editions, the last in 1866, and which was far superior to the three American textbooks that had preceded it He was well thought of by his colleagues outside of Boston, as evidenced by the fact that he was one of the original members of the American Ophthalmological Society and its president from 1869 to 1873 He was president of the Massachusetts Medical Society in 1880 and was a fellow of the American Academy of Arts and Sciences, unusual honors for an ophthalmologist He was a member of several exclusive social clubs in Boston and a member of the Eastern Yacht Club Nevertheless, he was heartily disliked by his ophthalmologic colleagues in Boston I have no printed evidence to this effect, but my information comes by word of mouth from a source in which I have complete confidence From the same source I learn that the cause of this animosity was not jealousy on the part of his colleagues, but an autocratic attitude on the part of Williams The facts that he was not a member of the New England Ophthalmological Society, organized in 1884, and that he was never on the staff of the Massachusetts Eye and Ear Infirmary accord with this information That he could make remarkable headway in spite of such local hostility is additional evidence of his great professional ability

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<sup>6</sup> Williams, H W A Practical Guide to the Study of the Diseases of the Eye Their Medical and Surgical Treatment, Boston, Ticknor & Fields, 1862

Other prominent American ophthalmologists of the past century were Edward L. Holmes (1828-1900), Cornelius Rea Agnew (1830-1888), Herman Jakob Knapp (1832-1911), Henry Drury Noyes (1832-1900), Simon Pollak (1832-1913), George T. Stevens (1832-1921), John Green (1835-1913), Hasket Derby (1835-1914), George C. Harlan (1835-1909), Edward G. Loring (1837-1888), David Bennet St. John Roosa (1838-1908), William Fisher Norris (1839-1901), Emil Gruning (1842-1914), Leartus Conner (1843-1911), F. K. Hotz (1843-1908), Samuel Theobald (1846-1930), John E. Weeks (1853- ), Charles H. Beard (1855-1916), Edward Jackson (1856-1942), Casey A. Wood (1856-1942), Alexander Duane (1858-1926), George E. de Schweinitz (1858-1938), and William C. Posey (1866-1934). There were many less well known ophthalmologists whose accomplishments, I am sure, were as great as, or greater than those of some of the men just listed.

The examples set by most of these prominent ophthalmologists as to devotion to their specialty, hard work and ethical conduct served to raise the standards of ophthalmology in this country. Probably highest in the esteem of their colleagues were Knapp, de Schweinitz and Jackson. Knapp was born in Germany and received his ophthalmologic training there. Leaving, at the age of 38, a professorship in Heidelberg, he moved to New York in 1868, where he spent the rest of his long and productive life. He gained prompt recognition as the preeminent ophthalmologist in America and did much to improve the status of his specialty here. He also specialized in otology, but not in laryngology. He founded a hospital, the New York Ophthalmic and Aural Institute, and also a journal, the *Archives of Ophthalmology and Otology* (1869), which, except for the short-lived and ill-famed first *American Journal of Ophthalmology*, published by Julius Homberger, was the first ophthalmologic journal in America. The *Archives* has never been exceeded in importance by any other American ophthalmologic journal and has greatly contributed to the progress of ophthalmology in this country. In 1879 the *Archives of Otology* was separated from it.

De Schweinitz was lavishly endowed both physically and mentally. He had an imposing, yet charming, personality and was the handsomest ophthalmologist I have ever known. He was the most fluent speaker I have ever heard, and at the same time one of the clearest. He had a thorough knowledge of ophthalmic literature and often called on this at a moment's notice in discussing papers at medical meetings. He gained such wide recognition that he was elected president of the American Medical Association in 1916. In spite of his many distinctions, he was unassuming in his attitude and was generous in his praise of his colleagues. If he was lacking in any desirable qualities, they were dexterity and originality.

Jackson had the welfare of ophthalmology deeply at heart and did much to further it. The American Board of Ophthalmology was his

branchchild, as I shall explain later. As editor of the *American Journal of Ophthalmology*, he performed for many years valuable service. His broad knowledge of the sciences basic to ophthalmology was impressive and was often manifested in his editorials. Thus, although he had no first hand knowledge of pathologic anatomy, he had in some way acquired a remarkably accurate understanding of this subject.

Most of the eminent American ophthalmologists who have been in active practice within the past fifty years I have had the pleasure of knowing personally. But, of the older men, the one I knew best and to whom I am indebted for my initiation into ophthalmology was Samuel Theobald. He was the first professor of ophthalmology at Johns Hopkins Medical School, and I was his first pupil to become an ophthalmologist. He was the leading ophthalmologist and otologist in Baltimore and was elected president of the American Ophthalmological Society in 1910. I never heard him display any pride in his own accomplishments, but he often proudly referred to his grandfather, Nathan R. Smith. Theobald made two valuable contributions to ophthalmology. One was his demonstration that stricture of the lacrimal duct could be permanently overcome by the repeated insertion of very large probes. At each visit the probe was left in place for about thirty minutes, so that in his waiting room there was almost always the alarming spectacle of at least one patient with a probe protruding from the region of his eye. He taught some patients to probe their own ducts. I can vouch for the fact that this treatment was eminently successful, curing not only the chronic dacryocystitis but also the epiphora. The method, however, has never come into general use, doubtless for the reason that few ophthalmologists have been bold enough to use such large probes, or persuasive enough to induce patients to continue the treatment. Theobald's other valuable contribution was his discovery of what, for the lack of a better term, he called subnormal accommodation in young persons. He meant by this that the range of accommodation was diminished but that in certain persons so much effort was required to accommodate that it caused a considerable degree of esophoria at the reading distance. He found that the resulting discomfort was completely relieved by the use of presbyopic glasses. Today this condition seems to be generally neglected.

Three national ophthalmologic societies, the American Ophthalmological, the Section on Ophthalmology of the American Medical Association, and the American Academy of Ophthalmology and Otolaryngology, have reflected the progress of ophthalmology in this country and, in fact, have also greatly contributed to it. The American Ophthalmological Society was conceived by and organized in 1869 by the efforts of Henry D. Noyes, of New York, and Hasket Derby, of Boston. This was the first special medical society in America, and the second in the world. Although many important papers have been presented at its meetings, I think its major contribution to ophthalmology has been its high requirements for mem-

bership Ever since its inception these requirements have included excellent professional performance and adherence to the highest professional ethics Membership in the society has therefore been a laudable ambition for the young and a gratifying reward for the older ophthalmologist Since it is human to err, the society has made mistakes of omissions and commissions in regard to membership, but these have been remarkably few

Although at the meeting in 1863 the American Medical Association recognized ophthalmology as a distinct specialty, it included this in the Section on Surgery and Anatomy until 1878, when a section for ophthalmology, otology and laryngology was organized and called Section 6 Herman Knapp, on motion of Eugene Smith, of Michigan, was elected chairman This election shows the rapidity with which Knapp had gained the high regard of his colleagues in his adopted country At the Section's first meeting, covering three days, there were six papers relating to ophthalmology, three of which were on cataract operations, two papers relating to otology and one relating to laryngology No transcripts of the discussions were kept, but in the minutes Knapp was mentioned as taking part in the discussions In addition, he read his chairman's lengthy address on the progress of ophthalmology and otology, a paper on cataract operations and another on mastoid operations and demonstrated several microscopic specimens of the eye and one of a tumor of the acoustic nerve It would seem that Knapp took a prominent part in the meeting, to say the least

In 1888 the American Medical Association divorced ophthalmology from the other specialties and gave it a section all its own I think it is fair to say that this section has been more progressive and original than any other section in the Association Thus, in 1891, Leartus Conner, in his chairman's address, was the first to propose that each section publish its own transactions in a separate volume This proposal was at once adopted by his own section Previously, the transactions of all the sections had been included in the published transactions of the American Medical Association until the advent of *The Journal of the American Medical Association*, in 1883, when they were published in this Incidentally, it may be mentioned that Samuel D Gross, a part time ophthalmologist, suggested as far back as 1869 that the American Medical Association publish a journal Conner also proposed two other innovations that were adopted, the election of the chairman by the section itself and the formation of an executive committee, such as we now have

In 1905 this section originated a procedure of publishing the papers in advance of the meeting This procedure had much merit, since it ensured better discussions, but was discontinued in 1932 on account of the expense involved and the difficulty of getting the volume printed before the meeting However, in dying, the pre-session volume left two important offspring, namely, the printing of full abstracts in the program, and

the selection of two speakers in advance to open the discussion of each paper

Another innovation by this section was the establishment, in 1910, of the Knapp testimonial fund and the Knapp Medal, at the original suggestion of W C Posey. The medal was to be awarded to the author of the best paper presented at a meeting, provided the paper was of sufficiently high merit. The first award was made in 1914 to Clifford B Walker. That a rather high standard has been set for the award is indicated by the fact that it has been made only eight times. Still another innovation was the establishment of the Ophthalmic Research Medal, at the suggestion of Lucien Howe, who in 1924 donated a fund of \$1,500 to provide for it. This medal has been awarded ten times, the first recipient was Edward Jackson, in 1926, the second, George de Schweinitz, in 1927. It is noteworthy, and I think praiseworthy, that the Section did not designate this medal by the name of the donor. To have done so might have suggested that the Knapp medal was donated by Knapp.

An important enterprise sponsored by this Section and the other two national ophthalmologic Societies is the Registry of Ophthalmic Pathology at the Army Medical Museum. This was established in 1922, chiefly through the efforts of Harry Gradle and the cooperation of Major G R Callender. It has partly overcome the distressful, not to say disgraceful, waste of pathologic eye material in this country, and is now a rich storehouse of sections of the eye. This was the first registry at the Army Medical Museum, and not until several years later was the first of the numerous other registries organized.

Perhaps the greatest single achievement of this Section was the part it played in establishing the American Board of Ophthalmology. The father of this board was Edward Jackson, the mother was this Section, while the American Academy of Ophthalmology and Otolaryngology and the American Ophthalmological Society were foster parents. Jackson, in 1915, suggested such a board in a committee report to this Section, and through the joint action of the three societies the board was organized in 1916, with Jackson as chairman. For many years afterward W H Wilder was the prime factor in making the Board a success—in fact it became his “baby.” If it is true that imitation is the highest compliment, then our Section has been complimented to an extreme degree, for most, if not all, the other specialties have since organized certification boards, albeit rather belatedly.

Being to a great extent hamstrung by the rules of the American Medical Association our Section, in comparison with independent societies, has been handicapped as regards setting of dues and assessments. However, as regards most other matters its progressive spirit has been unrestrained. Whenever a debatable question has arisen, our Section has promptly appointed a committee to answer it. Only occasionally has a committee forgotten to bring in a report.

There is one way, however, in which our Section is a laggard, not as compared with other sections, but as compared with independent ophthalmologic societies. I refer to the failure to require certification by the American Board of Ophthalmology as a qualification for voting membership. I hope ours will take the lead over all other sections of the American Medical Association, as it has in so many other matters, in urging the powers that be to adopt such a requirement. This need not, in fact, should not, bar any member of the American Medical Association from attending section meetings or from presenting a meritorious paper before any section.

The American Academy of Ophthalmology and Otolaryngology was organized in 1896 under the name of the Western Ophthalmic and Otolaryngologic Society, with Adolf Alt as the first president. In 1903 its name was changed to the present one. Its purpose was to serve the interests of men who combined all three specialties in their practices. This combination, obviously, was based on business reasons, not on similarities or overlapping fields, for ophthalmology is more closely related to neurology, or even to dermatology, than it is to otology or laryngology. At first the membership of the Academy consisted chiefly of midwesterners, but within recent years it has attracted to its fold most of the eastern ophthalmologists and now includes about all the eminent specialists in diseases of the eye, ear, nose and throat of the country. This may be partly because from the standpoint of scientific activities it really consists of two separate societies, which meet at the same time and place. The popularity of the Academy has been greatly enhanced by its instructional courses. So far as I know, it was the first medical society to institute such courses. Whenever I question a member returning from a meeting of the Academy, he always states that he gets more out of these meetings than out of those of any other society.

Another national society, the Association for Research in Ophthalmology, organized in 1929, perhaps before there was real need for it, is growing in importance and will no doubt soon firmly establish a unique place for itself, largely because it attracts and admits to membership investigation without medical degrees.

It is noteworthy that the first International Ophthalmological Congress, held in Brussels in 1857, antedated all national ophthalmologic societies. The representatives from the United States were Gross, Hays, Lazarus and Littell. The Congress has met in America only twice. In 1876 it was held in New York, and E. Williams, of Cincinnati, was elected president. In 1922 it was held in Washington, with de Schweinitz as president.

In addition to the national societies, fifteen sectional and numerous state and local ophthalmologic societies have sprung up all over the country and have contributed mightily to the progress of American ophthalmology. Time will not permit me to describe even those centered in New York, Philadelphia and Boston.



The following journals, now defunct, have played more or less important parts in the development of ophthalmology in this country *American Journal of Ophthalmology* (1884-1917), *Ophthalmic Record* (1891-1917), *Annals of Ophthalmology* (1892-1917), *Ophthalmology* (1904-1916), *Ophthalmic Literature* (1911-1922) and *American Journal of Physiological Optics* (1920-1926) The *American Journal of Ophthalmology*, an entirely new journal, with an old name and with Edward Jackson as editor, took the place of the three journals discontinued in 1917

Until within recent years, the ophthalmologist in this country either was largely self taught so far as his specialty was concerned or obtained his first special training abroad, notable in Vienna, Berlin or London For years Vienna was the Mecca for American would-be ophthalmologists Those who studied there could be divided into three classes, those who had failed to obtain an internship in America, those who sought the prestige connected with foreign study and, those who were chiefly motivated by the desire to obtain the best possible training Those in the third class were fewest, but generally remained abroad the longest

Until within about the past ten years, even the man who obtained an ophthalmic internship in this country was largely self taught He was seldom taught anything by the staff of the hospital or required to learn much The internship, however, gave him an excellent opportunity to teach himself I am inclined to believe that the self-taught ophthalmologist is the best taught provided his teacher has high intellectual qualifications and adequate clinical and laboratory facilities As anticipated by its founders, the American Board of Ophthalmology has indirectly improved the teaching of ophthalmology by creating a demand ignorance of physiologic optics also still prevails

Forty years ago it was difficult to find a prominent American ophthalmologist, or even a professor of ophthalmology, who had any real knowledge of such basic subjects as physiologic optics or ophthalmic pathology On the other hand, on the European Continent it was difficult to find any ophthalmologist who did not have such knowledge I can recall that in those days, when an attempt was made to show almost any prominent American ophthalmologist a microscopic section, he would approach the microscope with his hands behind his back, displaying no desire to change the focus of the instrument or to adjust the slide In fact, he would approach the instrument as though he feared it might bite him You may expect me to say that conditions have now vastly changed, but I must disappoint you American ophthalmologists sufficiently familiar with ophthalmic pathology to interpret or describe a microscopic section of a diseased eye are still extremely few And almost equally as widespread ignorance of physiologic optics also still prevails

During the past one hundred years the progress of ophthalmology has exceeded that within all previous centuries combined Time will permit

me to mention only the outstanding achievements. The ophthalmoscope, perimeter, ophthalmometer, photometer, tonometer, electric magnet for removing foreign bodies, binocular corneal microscope, slit lamp and camera for fundus photography have been invented. Iridectomy, various filtration operations and cyclodialysis, for glaucoma, and operations for strabismus and for separation of the retina have been devised. The use of cocaine for local anesthesia, the prophylactic use of silver nitrate to prevent gonorrheal conjunctivitis in infants and the use of miotics to control glaucoma have been brought forward. Many diseases of the external and internal eye have been discovered, named and classified. Important discoveries relating to the normal and pathologic histology of the eye, and to the bacteriology of the eye have been made. Neuro-ophthalmology has been developed.

The sad fact must now be recorded that not one of these contributions, nor any other ophthalmologic contribution of fundamental importance has originated in America. The ambition of American ophthalmologists has generally soared no higher than the attainment of the practical knowledge developed by their foreign colleagues. Nevertheless, American ophthalmologists have made to the advancement of their science many contributions of minor importance, and a few of considerable importance. Notable among the latter are Weeks's discovery of his bacillus (1886), Bail's report of the first case of conjunctivitis proved to be caused by *Pasteurella tularensis* (1914), Horner's discovery of a small muscle at the inner canthus (1824), Hasket Derby's discovery that mydriatics may precipitate an attack of glaucoma (1866), Holden's discovery of the cause of the red spot in the macula in amaurotic family idiocy (1898), Stevens' invention of the terms heterophoria, exophoria, etc. (1886), Duane's subjective parallax test for heterophoria (1889), Williams' corneal suture after cataract extraction (1886), H. B. Chandler's peripheral iridectomy (buttonhole) for cataract operations (1890), Wadsworth's slanted mirror for the ophthalmoscope (1877), Loring's ophthalmoscope with hinged mirror (1877), Dennett's electric ophthalmoscope (1885), Knapp's knife needle and his roller forceps, Hays's needle knife, Ziegler's knife needle, Noyes's scissors, Murdoch's speculum (1883) and Prince's advancement forceps. Also should be mentioned here the fact that Phillip Syng Physick was the first to suggest (1816) the use of absorbable sutures made of animal tissues. A notable American contribution to ophthalmology, although not by an ophthalmologist, was the invention of bifocal glasses in 1784 by Benjamin Franklin.

To name the bacillus discovered by Weeks the Koch-Weeks bacillus is unfair to Weeks. It is true that Koch had previously observed a similar bacillus in exudates from trachomatous eyes, but he had regarded it as a contaminating organism of no importance. Weeks, on the other hand, showed that his bacillus was the cause of a special form of conjunctivitis.

Henry W Williams was the first to suture the wound after cataract extraction. He employed a single corneal suture, which he described in 1866, but, although he continued to advocate its use, it apparently was never adopted by any other surgeon. This may be because it had the serious fault of passing entirely through the cornea. However, sutures somewhat like that of Williams' are now coming into general use in cataract surgery.

Barraquer is generally given the credit for the method of removing the lens in capsule by the aid of a suction cup, although Hulen, of New York, described the method in 1910, seven years before Barraquer did so. However, this country cannot take credit for this operation, since essentially the same procedure was described by Stoevei in 1902. Nor can this country claim the operation now termed goniotomy. This has been perfected here but was devised by de Vicentius in 1892. It was one of Haab's favorite operations for chronic glaucoma. He termed it anterior sclerotomy and in 1905 stated it was the best operation for infantile glaucoma. Vogt, in 1925, claimed the credit for originating the operation of cyclodiathermy. However, two Americans, in 1921, reduced intraocular pressure by applying destructive heat to the corneal limbus and therefore to the ciliary body.

According to the opinions of numerous American ophthalmologists who have visited foreign clinics, the best of our ophthalmic surgeons have been for many years more skilful than the best European surgeons. To explain this superiority, I assume that as a result of our diversity of population some of our surgeons have inherited an unusual degree of dexterity. On the other hand, a claim that our worst ophthalmic surgeons are the worst in the world might be difficult to refute.

Soon after the publication in 1866 of Donder's work on refraction, American ophthalmologists began to busy themselves with this subject, and by the end of the century had become expert in the determination of refractive errors. Following the lead of Weir Mitchell, a neurologist, many convinced themselves that uncorrected or improperly corrected refractive errors not only often caused headaches and ocular discomfort but caused or contributed to a variety of other symptoms, and even to organic disease. They did not devise any basically new methods of testing, but applied with meticulous care methods already known. It was believed that astigmatism of  $\frac{1}{8}$  D could cause serious so-called eyestrain. Although severely exposed to this virus in my ophthalmologic infancy, I escaped infection. This may be because I was born in Kentucky, a state that borders on Missouri. The term eyestrain was undoubtedly invented in this country, but just when and by whom I do not know. If it has no other merit, it has that of satisfying patients. Their idea of what it means is indicated by such questions as, "Doctor do you find my eyes badly strained?" I suspect that it was the overemphasis placed by

ophthalmologists on the importance of refractive errors that has led to the present unsatisfactory conditions relating to optometry. From what I have said, I hope no one will get the impression that I condone inaccurate refraction. In my own opinion, and in that of some of my patients, no one corrects refractive errors more precisely than I do.

Many excellent treatises dealing with ophthalmology have been published in this country. Among these may be mentioned textbooks by H. W. Williams,<sup>6</sup> 1862, by Noyes,<sup>7</sup> 1881, and 1890, by de Schweinitz,<sup>8</sup> 1892, by Weeks,<sup>9</sup> 1910, "Skiascopy, and Its Practical Application," by Edward Jackson,<sup>10</sup> 1895, "System of Diseases of the Eye," edited by Norris and Oliver,<sup>11</sup> 1897-1900, "The American Encyclopedia and Dictionary of Ophthalmology," edited by Casey A. Wood,<sup>12</sup> 1913-1921, "The Eye and the Nervous System," edited by Posey and Spiller,<sup>13</sup> 1906. These books all served useful purposes in America, and some "filled a long-felt want," but it must be admitted that none of them quite reached the highest European standards.

In view of the great wealth of this country and the strong appeal made by blindness, it is remarkable how little has been donated to ophthalmic hospitals and for ophthalmic research. The Wilmer Institute, opened in 1924, and the Howe Laboratory of Ophthalmology, organized in 1931, were the first institutions in America especially endowed for ophthalmic research, and their endowments are still relatively inadequate. Now that government is preventing the accumulation of great private wealth, it may take over the financing of many institutions formerly largely dependent on private donations. That this is a desirable consummation is questionable.

During the past century this country has passed through five important wars, but separate ophthalmic departments in medical services were organized only in the two world wars. The ophthalmologists who manned these departments in each war were volunteers, not draftees. For the great sacrifices these men made, it cannot be said that on their return to civilian

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7 Noyes, H. D. A treatise [on] Diseases of the Eye, New York, W. Wood & Co., 1881, A Text-Book on Diseases of the Eye, *ibid.*, 1890.

8 de Schweinitz, G. E. Diseases of the Eye. A Handbook of Ophthalmic Practice, for Students and Practitioners, Philadelphia, W. B. Saunders Company, 1892.

9 Weeks, J. E. A Treatise on Diseases of the Eye, Philadelphia, Lea & Febiger, 1910.

10 Jackson, E. Skiascopy, and Its Practical Application to the Study of Refraction, Philadelphia, Edwards & Docher Co., 1895.

11 Norris, W. F., and Oliver, C. A. System of Diseases of the Eye, Philadelphia, J. B. Lippincott Company, 1897-1898.

12 Wood, C. A. The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1913-1917.

13 Posey, W. C., and Spiller, W. G. The Eye and the Nervous System, Philadelphia, J. B. Lippincott Company, 1906.

life they were overwhelmed by the gratitude of those who had remained at home. A truthful account of the efficiencies and inefficiencies of the ophthalmic services in the two world wars would no doubt be of considerable interest, but is beyond the scope of this address, since these services contributed nothing of importance to the advancement of ophthalmic science, greatly as they contributed to the welfare of our armed forces.

However much it hurts our pride, the fact that this our country has been greatly excelled by other countries in contributions to ophthalmology would not be deplorable did it not mean neglect of superior opportunities. What is the cause of this deficiency? Long ago, two former chairmen of this Section attempted to answer this question. Harold Gifford, in his chairman's address in 1898, maintained that the answer lay in the meager qualifications required of medical teachers in this country. He said, "I think it is no exaggeration to say, leaving the smaller institutions out of the question, that in the best twenty of our medical schools more than one-half of the professors taken in the aggregate have received their positions for considerations which in Germany would hardly entitle them to the rank of privatdocent." In 1907 Alvan A. Hubbell wrote

"Physicians and surgeons have seldom been paid for teaching or for serving a hospital. The result has been, therefore, that without such a living salary as is paid to those attached to government schools and hospitals of Europe, our American medical teachers and hospital attendants have had to earn their living outside in private practice, and in doing this it has consumed nearly or quite all of their time and energy."

It seems to me that although what each of these astute ophthalmologists said is still true, there is a more fundamental cause of the deficiency in question. This is revealed by consideration of the fact that the deficiency is not confined to ophthalmology but exists throughout the whole of American science. For while America has excelled in the application of basic scientific facts, few of these facts have been discovered in this country. The explanation obviously lies in the lack of true scientific spirit. To a man imbued with this spirit, his discovery of a new fact is of itself sufficient reward without the addition of public acclaim or pecuniary return. It was natural that in the early days of this country paramount importance was given to the accumulation of tangible wealth, but the resulting attitude of mind persists here even today and continues to impede the development of the scientific spirit.

Now World War II has thrust on the United States leadership in ophthalmology, as in all other branches of medicine. At present this is a stimulus to the progress of ophthalmology here. It is to be hoped that, in spite of political obstacles which many of us fear we foresee in the near future, this accelerated progress will continue without interruption.

# ATROPHY OF THE OPTIC NERVE DUE TO MALNUTRITION

Report of two cases

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Two cases of atrophy of the optic nerve, probably due to malnutrition, are reported, this complication of malnutrition may be commoner now than the literature has indicated in the past. This greater frequency may be incident to the severe malnutrition to which some American prisoners of war were subjected. A short review of the available literature is given.

Lombroso (1869), Guaita, Rampoldi and several other Italian authors, as cited by Bietti,<sup>1</sup> reported atrophy of the optic nerve in pellagrins, but, as Bietti pointed out, other reasons for the atrophy had not been ruled out. The principal object of Bietti's report was an investigation of the relation of pellagra to retinitis pigmentosa. Microscopic examination of the eyes of 10 patients who had died of pellagra did not reveal a single case of atrophy of the optic nerve.

Whaley<sup>2</sup> reported on examinations of 36 pellagrins, 3 of whom had optic nerve atrophy, but, again, this may have been a coincidence, and the changes in the disk may have been due to other causes.

Calhoun<sup>3</sup> discussed the etiology of pellagra. In agreement with Goldberger, who had conducted a controlled dietary experiment at a penitentiary, he concluded that pellagra was of dietary origin. He also discussed the systemic and ocular symptoms. He reported on 10 patients with pellagra who were not alcoholic, did not smoke and were not addicted to the use of drugs. He accompanied the article with illustrations of their visual fields. The peripheral fields showed contraction for form and color, the central fields, absolute and relative scotomas for color. Examination of the fundus did not show hemorrhages but revealed temporal pallor and atrophy of the optic nerve in some patients.

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1 Bietti, A. Ueber Augenveränderungen bei Pellagra, *Klin Monatsbl f Augenh* 39 337, 1901.

2 Whaley, E. M. Eye Symptoms of Pellagra, *Tr Nat Conf on Pellagra* 1 279, 1909.

3 Calhoun, F. P. Alterations in the Visual Fields associated with Pellagra, *Am J Ophth* 1:834 (Dec) 1918.

In a discussion of beriberi, Elliot<sup>4</sup> summarized the ocular symptoms as those due to retrobulbar neuritis (central scotomas, diminution of central visual acuity and changes in the peripheral visual field), second, those due to paralysis of the muscles of the eye, including ptosis, and, third, decreased sensibility of the cornea. He pointed out that the fundus may present one of three appearances: no pathologic change, atrophy of the papillomacular bundle or atrophy of the whole disk. He reported that central vision hardly ever falls below 20/200. In his review of pellagra, Elliot mentioned the systemic and the ocular changes: asthenopia, circulatory changes in the retinal vessels, night blindness, amblyopia, atrophy of the optic nerve, cataract and pareses of the ocular muscles.

Cronin<sup>5</sup> reported a case of pellagra with ocular disturbance and psychosis in a patient 37 years old with chronic alcoholism. Vision was 20/200, not correctible, in the right eye and 20/20—2, corrected to 20/15, in the left eye. There was a central scotoma of the right eye, with no changes in the peripheral fields. Funduscopy showed a macular hemorrhage and temporal pallor. On reexamination at a later date, vision proved to be nearly normal. Syphilis or multiple sclerosis was considered, but the anemia of pellagra was assigned as the most likely cause of the macular hemorrhage.

Levine<sup>6</sup> reported the case of a white woman aged 47, who was chronically alcoholic and exhibited all the cardinal symptoms and signs of pellagra, including greatly impaired vision, bilateral optic neuritis and cecentral scotoma in both eyes. With a high protein diet and treatment with riboflavin, the patient made an excellent recovery. The author discussed the etiologic role of riboflavin, quoted J. H. Smith and pointed out the importance of an adequate sulfur intake (especially in the form of cystine) and normal sulfur metabolism as protection against solar radiation. He cited statistics showing the frequency of pellagra in the southern United States. He described the symptoms, pathologic features, treatment and prognosis of pellagra, with special attention to the ocular symptoms.

Carroll<sup>7</sup> reported on 10 patients, all chronically alcoholic and suffering from various degrees of visual impairment. Some patients had vision limited to counting fingers at 3 feet (90 cm) and showed changes in the visual fields accordingly. These patients had pellagra or polyneuritis or both. When an antipellagra regimen was instituted, the patients showed

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4 Elliot, R. H. *Tropical Ophthalmology*, London, Oxford University Press, 1920.

5 Cronin, H. J. *Pellagra with Ocular Disturbances and Psychosis*, *J. Nerv. & Ment. Dis.* **78**: 35 (July) 1933.

6 Levine, J. *Pellagra as a Cause of Optic Neuritis*, *Arch. Ophth.* **12**: 902 (Dec.) 1934.

7 Carroll, F. D. "Alcohol" Amblyopia, Pellagra, Polyneuritis, *Arch. Ophth.* **16**: 918 (Dec.) 1936.

striking improvement in visual acuity, visual fields and general condition, most of them regaining normal vision

Fine and Lachman,<sup>8</sup> in an excellent article, reviewed the literature and reported on 3 patients, all alcoholic and pellagious, who had impaired vision due to retrobulbar neuritis. In addition to the cutaneous and systemic symptoms, the patients showed impaired visual acuity, not correctible with glasses. With intensive vitamin therapy, the vision of 2 patients returned to normal and was greatly improved in the third. The fields showed chiefly central changes for white and colors, these also improved with therapy. Some patients exhibited temporal pallor of the disks. The relation of pellagra to polyneuritis, on the one hand, and to chronic alcoholism, on the other, was pointed out. Cowgill<sup>9</sup> and Jolliffe and associates<sup>10</sup> stated that the important etiologic factor is a deficiency in thiamine and riboflavin, the latter deficiency probably affecting the central nervous system. The 2 cases to be reported in this paper seem to offer evidence in favor of this hypothesis.

Beam<sup>11</sup> summarized the cases of 8 white men from 20 to 32 years of age. All these patients had been prisoners of the Japanese and had suffered from severe malnutrition during their confinement. They had received about 1,000 calories daily, with minimal amounts of protein and vitamins. These patients had a visual acuity of 1/200 to 10/200 in the better eye. All had bilateral central scotoma, and 2 patients showed concentric contraction of the fields. Funduscopic examination showed bilateral atrophy of the optic nerve. It is concluded that three etiologic factors may have been involved: a deficiency in vitamins, minerals and protein; intoxication of a chemical or bacterial nature, and the effect of strenuous physical work with inadequate caloric intake. He concluded, however, that the most important factor was a deficiency in thiamine.

#### REPORT OF CASES

CASE 1—A white man aged 39 had been in perfect physical condition until about February 1942. In 1941 he was sent to the Philippines. At that time his vision was normal.

With the outbreak of the war, his food rations became very short. This poor diet apparently caused him to feel tired and weak for several weeks before his capture, on April 9, 1942. He was a prisoner of war until his liberation, in

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8 Fine, M., and Lachman, G. S. Retrobulbar Neuritis in Pellagra, *Am J Ophth* **20**:708 (July) 1937.

9 Cowgill, G. R. *The Vitamin B Requirement of Man*, New Haven, Conn., Yale University Press, 1934.

10 Jolliffe, N., Colbert, C. N., and Joffe, P. M. Observations on Etiologic Relationship of Vitamin B ( $B_1$ ) to Polyneuritis in Alcohol Addict, *Am J M Sc* **191** 515 (April) 1936.

11 Beam, A. D. Amblyopia Due to Dietary Deficiency, *Arch Ophth* **36** 113 (March) 1946.



February 1945 In May 1942 he seems to have had bacillary dysentery, causing severe weakness This was treated successfully with sulfonamide drugs In July 1942 he had jaundice and cystitis, lasting several months The patient believes that in August 1942 he had "wet beriberi," characterized by edema of the face and severe pain with edema of the extremities In August 1943 scurvy also developed, which was characterized by ulcers of the mouth and was improved by his eating a few limes At the same time the patient apparently had pellagra, manifested by red, scaly, rough areas on the backs of his hands

During July and August 1942 the patient noted a mild decrease in his visual acuity, the loss being equal in the two eyes This became worse during September 1942, at which time he could see only the ground and moving objects, without being able to identify the latter This severe impairment lasted until December 1942 The patient was transferred to a different camp in November 1942, and there the diet contained sufficient rice, vegetables and fruit He was hospitalized but did not receive vitamin medication He ascribes an improvement in his vision one month after his arrival in this new camp to the better diet

In December 1942 the patient had his first attack of malaria, these attacks recurred monthly for the next ten months Each attack was treated with quinine, which later was given prophylactically for many months In April 1943 pronounced deafness developed In August 1944 a diagnosis of dengue was made From July 1944 on, the patient received intensive vitamin therapy and noted pronounced improvement in all his symptoms, although the caloric intake was less than before

Shortly after the patient's liberation, in February 1945, the following diagnoses were made at an Army installation malnutrition, beriberi, tinnitus aurium, and atrophy of the optic nerve, with vision of 20/400 bilaterally

The patient was placed on a high caloric, high vitamin diet and was given high doses of preparations of vitamins A and D, ascorbic acid, riboflavin, nicotinic acid thiamine and the vitamin B complex Throughout this hospitalization he was given physical and occupational therapy The blood counts were normal, and smears revealed no malarial organisms The sedimentation rate was increased at first but became normal after several months The urine and albumin-globulin ratio were normal and cultures of the stools yielded no pathogens The serologic reactions were negative Electrocardiograms were normal Roentgenologic examination of the chest showed no pathologic changes

Reexamination about one year after his liberation showed notable improvement, use of the lower extremities, however, was still greatly impaired

Ophthalmologic examination showed vision of 5/200 in each eye and bilateral atrophy of the optic nerve A central scotoma was present in each eye

When the patient was last examined, in December 1946, his general condition had further improved but he was unable to get around without a cane

Vision was 20/200 in the right eye and 10/400 in the left eye, not correctible in either eye External examination of the eyes showed nothing unusual Examination with the slit lamp revealed a small scar from a foreign body in each cornea Fundusoscopic studies revealed nearly identical pictures in the two eyes The disk was well outlined, with a small physiologic excavation, the temporal third of each disk was extremely pale with a greenish tinge, the lamina cribrosa was not seen, the blood vessels showed a slight increase in connective tissue for a distance of about  $\frac{1}{4}$  disk diameter from the disk, adjacent to the temporal margin of the disk, there was an area of decreased retinal pigment, bordered temporally by a slight increase in pigment, the macula showed a central reflex and, like the rest of the fundus, showed no pathologic change

The visual fields were difficult to take, since the patient was unable to fixate. For the peripheral fields, his forefinger was placed on the fixation point, and for the central fields, which were taken on the Lloyd stereocampimeter, he was instructed to look at the center of the circles. He was unable to see even the largest target in the center of the field.

The patient's peripheral fields, taken with a 4 mm white target at 330 mm, showed slight contraction. The fields for blue and red were also slightly contracted and showed central scotomas, with a radius of somewhat less than 10 degrees and of identical size, for blue and red. Green was not recognized as such in any part of the field. Six targets were used on a 330 mm perimeter. Bilateral central fields for 1 degree white showed a large cecocentral scotoma extending between 15 and 20 degrees in the upper field and to about 5 degrees in the lower field, these boundaries conforming to the path of the nerve fibers. All fields were taken with full illumination.

The ophthalmologic diagnosis was bilateral severe atrophy of the optic nerve, this was probably due to severe malnutrition and avitaminosis. The appearance of the disk suggested that the atrophy was preceded by optic neuritis.

CASE 2—A white man aged 38 was well at the time of his capture on Bataan, on April 9, 1942. Early in 1942 his diet became poor and remained inadequate until his liberation, in September 1945. At the end of April 1942 he noted edema of the ankles, which disappeared during a severe attack of diarrhea early in May 1942. About the end of this month he had malaria, which was treated with quinine. Loss of weight at that time was about 55 pounds (24.9 Kg). During July and August 1942 numbness of the toes developed, and during October 1942 he experienced pain in the toes, feet, ankles and legs up to the knees. At this time, also, there developed ulcers of the mouth and peeling of the skin of the scrotum. During the latter part of December 1942 the pain in the lower extremities became gradually worse, until it kept the patient awake at night. About January 5 or 6, 1943, vision failed suddenly and severely, the loss being about the same in the two eyes. The patient was transferred to a new camp, where the diet was much better for several months and he gained 2 or 3 pounds (0.9 or 1.3 Kg) a month. Several months after the improvement in his diet he noted that his vision gradually became better. This improvement lasted three months, after which his vision became somewhat worse again, this deterioration coincided with a change for the worse in his diet. From then on, his vision remained stationary.

The patient had a few more attacks of malaria between February 1943 and October 1944 and continued to show systemic signs of malnutrition, but there was no further deterioration in vision. He was liberated on Sept 8, 1945. Thereafter, he received a high vitamin diet and regained the weight he had lost.

Physical examination on admission revealed nothing abnormal. The ophthalmologist stated in November 1945 that the patient showed partial atrophy of the optic nerve, secondary to retrobulbar neuritis caused by malnutrition. The patient received high vitamin medication and symptomatic therapy. Another ophthalmologic examination, three months later, revealed no change. A third examination of the eyes, about five months later, in July 1946, showed vision of 20/100 in each eye, which was not correctible. External examination of the eyes showed nothing pathologic. Extraocular movements and pupillary reactions were normal. Fundusoscopic examination revealed a similar condition in the two eyes. The media were clear, the disk was well outlined and round, with a small physiologic excavation, and showed temporal pallor, the pale area involving the entire temporal half and having a greenish tinge, the blood vessels were normal, the macula showed no abnormality except for absence of the macular reflex, the retina was well pigmented,

and no other pathologic condition was seen. Examination with the slit lamp revealed nothing abnormal except for prominence of the corneal nerves and slight bulging of the right iris near the angle, in the 180 degree axis. The central fields showed bilateral absolute central scotoma nearly 2 degrees in size, which covered the fixation point. Temporal to the absolute scotoma, and continuous with it, was a sickle-shaped relative scotoma, extending another 2 degrees. Thus, it looked as though the central scotoma was reaching for the blindspot. The peripheral field was normal in both eyes.

To rule out retrobulbar neuritis with an etiologic basis other than malnutrition, the following work-up of the case was made. Otorhinolaryngologic examination showed no focus of infection, reactions to the test with purified protein derivative were negative after twenty-four and forty-eight hours, a consultant in genitourinary diseases found nothing abnormal, roentgenologic examination of all the teeth revealed no focus of infection, roentgenologic studies of the chest and paranasal sinuses and anteroposterior and lateral exposures of the skull showed no lesions, the spinal fluid was normal, agglutination tests gave negative reactions for typhoid, paratyphoid, undulant fever and *Proteus vulgaris* X19, repeated cultures of the stools yielded no pathogens, the serologic reactions were negative, the blood count and urine were normal, and special search for malarial parasites gave negative results.

A diagnosis of severe bilateral optic nerve atrophy was made, it was assumed that this was due to severe malnutrition and avitaminosis.

#### SUMMARY

The available literature on the relation between vitamin deficiencies and optic nerve atrophy is briefly reviewed.

Two cases are presented. A detailed history is given in order to show that the visual difficulties were concurrent with other symptoms of vitamin deficiency and that the visual disturbances improved with an improvement in the diet.

No attempt is made to determine lack of which vitamin may have caused the atrophy of the optic nerve.

No attempt is made to determine whether the optic nerve atrophy was due to a primary disturbance in the ganglion cells of the retina, to optic neuritis or to retrobulbar neuritis.

## STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

### X The Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit

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AND

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BALTIMORE

The search for a chemical agent with a direct action on the tubercle bacillus began with the early observation of Koch that gold salts had an inhibitory action on the *in vitro* growth of the organism. Colloid of gold preparations were thereafter used clinically in the treatment of various tuberculous lesions, including laryngeal and ocular tuberculosis, and some encouraging results were reported. Untoward reactions, however, were so frequent, and sometimes of such severity, that in 1926 Calmette protested against the use of these preparations on the ground that the frequent deleterious effects greatly outweighed any favorable clinical action. Various dye preparations were later used in the treatment of ocular tuberculosis, but the reported results were not sufficiently encouraging to arouse any great enthusiasm for their use. In 1932 Wells<sup>1</sup> reviewed the literature on the chemotherapy of tuberculosis and concluded that of the many remedies proposed up to that time none had demonstrated the ability to arrest progress of a tuberculous infection either in man or in experimental animals. In recent years, however, the success achieved by various sulfonamide preparations in a wide variety of infections brought up the question of the possible use of some of these compounds in the treatment of tuberculosis. Interest in this possibility was especially stimulated by the report of Rich and Follis<sup>2</sup> in 1938. These authors reported

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1 Wells, H. G. The Chemotherapy of Tuberculosis, *Yale J. Biol. & Med.* **4**: 611 (March) 1932

2 Rich, A. R., and Follis, R. H., Jr. The Inhibitory Effect of Sulfanilamide on Development of Experimental Tuberculosis in the Guinea Pig, *Bull. Johns Hopkins Hosp.* **62**:77 (Jan.) 1938

that treatment with sulfanilamide, begun prior to inoculation, had an inhibitory effect on the development of tuberculosis in the experimental guinea pig. However, the clinical use of sulfanilamide on various tuberculous infections failed to reveal any therapeutic action, and until the reports of Feldman and his co-workers no sulfonamide compounds were found with any direct chemotherapeutic action in tuberculosis.

In 1940 Feldman, Hinshaw and Moses<sup>3</sup> reported on the action of a sulfonamide preparation—the sodium salt of p,p'-diaminodiphenylsulfone-N, N'-didextrose sulfonate, known as "promin," on experimental tuberculosis in the guinea pig. After this preliminary paper, there appeared a series of reports from these investigators on experimental studies relating to the action of various sulfonamide preparations in tuberculosis. Three sulfones were found which had a definitely deterrent action on the progress of established tuberculosis in the experimental guinea pig. These preparations were "promin," "diasone" (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) and "promizole" (4, 2'-diaminophenyl-5'-thiazolylsulfone, an isomer of sulfathiazole). The deterrent action of these drugs is best illustrated by summarizing a few of the experimental reports of Feldman and his co-workers. In one report<sup>4</sup> on the action of promin, Feldman and his co-workers stated that when "promin" was given guinea pigs beginning either on the day of injection or three days or one, two, four or six weeks after the date of infection, it had a deterrent action on the ensuing tuberculosis, i.e., at the end of six months all control animals were dead, whereas 84 per cent of the treated animals were living. Of the living animals, 43 per cent showed no histologic lesions of tuberculosis, whereas 57 per cent showed lesions in the visceral organs or elsewhere. A suspension of the spleen of 8 of 17 treated animals failed to produce lesions on reinoculation. The "promin" was found to be more efficacious if given continually, although it still had a strong effect when given intermittently. In 1943 Feldman<sup>5</sup> and Hinshaw suggested that "promin" might have either a direct action against the tubercle bacillus or an indirect action in that the resistance of the host was made more effective by a degradation of the virulence of the infecting agent. In a later experiment,<sup>6</sup> however, he found no evi-

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3 Feldman, W. H., Hinshaw, H. C., and Moses, H. E. The Effect of Promin on Experimental Tuberculosis. Preliminary Report, Proc. Staff Meet., Mayo Clin **15** 695 (Oct. 30) 1940.

4 Feldman, W. H., Hinshaw, H. C., and Moses, H. E. Promin in Experimental Tuberculosis, Am. Rev. Tuberc. **45** 303 (March) 1942.

5 Feldman, W. H., and Hinshaw, H. C. Promin in Experimental Tuberculosis, Am. Rev. Tuberc. **48** 256 (Oct.) 1943.

6 Feldman, W. H., and Hinshaw, H. C. Promin in Experimental Tuberculosis, Am. Rev. Tuberc. **51** 268 (March) 1945.

dence of an undue acquired resistance developing after treatment with "promin" The effect of "diasone"<sup>7</sup> was rather similar to that of "promin" Two hundred and eighty-eight days after treatment was terminated, 71 per cent of the control series were dead, whereas only 14 per cent of the treated group had died He concluded that "diasone" likewise had a deterrent effect and that it was a little less toxic than "promin," although both drugs produced definite toxic symptoms

"Promizole"<sup>8</sup> had a deterrent action similar to that of "promin," but was decidedly less toxic In one experiment, treatment with "promin" and "promizole" was commenced in two series of guinea pigs prior to inoculation The animals were then inoculated and the resulting disease was allowed to progress for sixty days, when the animals were killed The degree of tuberculous infection was evaluated on a numerical scale<sup>9</sup> The control group showed 66.4 per cent involvement, whereas the group treated with "promin" showed 4.4 per cent and the group treated with "promizole" 6.2 per cent involvement In a second experiment, guinea pigs were inoculated, and the resulting tuberculosis was allowed to progress for periods of from six to ten weeks before treatment was started At the end of two hundred and twenty-six days only 20 per cent of the control group survived, whereas 85 per cent of the group treated with "promin" and from 67 to 90 per cent of the group treated with "promizole" (depending on the time after infection that treatment was commenced) were still living A histologic assay of the amount of tuberculosis in the survivors showed 83 per cent in the control group, 10.8 per cent in the group treated with "promin" and from 16.4 to 33.8 per cent in the various groups treated with "promizole" Suspensions of the spleens of 14 guinea pigs treated with "promizole" and injected into normal pigs were found to be infectious in only 4 animals "Promizole" had a low toxicity and appeared to be an agent on the way to fulfilling the requirements of chemotherapy of tuberculosis

Despite these highly encouraging experimental reports, which have been confirmed by other observers,<sup>10</sup> the clinical use of these compounds has in the main been disappointing The present status has recently been

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7 Feldman, W. H., Hinshaw, H. C., and Moses, H. E. Therapeutic Effects of Disodium Formaldehyde Sulfoxylate Diaminodiphenylsulfone in Experimental Tuberculosis, *Arch. Path.* **36**:64 (July) 1943

8 Feldman, W. H., Hinshaw, H. C., and Mann, F. C. Promizole in Tuberculosis, *Am. Rev. Tuberc.* **50**:418 (Nov.) 1944

9 Feldman, W. H. Scheme for the Numerical Recording of Tuberculous Changes in Experimentally Infected Guinea Pigs, *Am. Rev. Tuberc.* **48**:248 (Oct.) 1943

10 Calloman, F. F. T. New Derivatives of Diaminodiphenylsulfone, *Am. Rev. Tuberc.* **47**:97 (Jan.) 1943.

well summarized by Hinshaw, Feldman and Pfuetze<sup>11</sup> A slight effect was obtained with "promin," but its toxicity limited its use "Promizole" had an extremely low toxicity, patients receiving 12 to 16 Gm per day with little or no reaction, but it had no effect on renal tuberculosis, failing to eradicate the bacilli from the urine of any of 10 patients for whom it was used It had no effect in 5 patients with tuberculous meningitis or in 2 patients with miliary tuberculosis Encouraging results were reported in cases of extrapulmonary infection, cutaneous tuberculosis, tuberculous lymphadenitis and tuberculous sinusitis The reports on "diasone" were conflicting, Petter and Prenslau<sup>12</sup> obtaining encouraging results, whereas Pfuetze<sup>13</sup> found no convincing action The drug was definitely toxic

In their summary of the experimental and clinical results, Feldman and his co-workers stressed the need of more rapid methods of forecasting the chemotherapeutic possibilities of new compounds They stated that in vitro studies were far from conclusive and that the experimental studies were open to the criticism that tuberculosis in the guinea pig is quite different from the disease in man

In the light of the experimental results obtained by Feldman and his co-workers, it seemed worth while to study the effect of these sulfones on ocular tuberculosis The reasons for such a study are twofold First, the eye is a most favorable site for observing the chemotherapeutic effect of a drug, it permits accurate clinical observation and evaluation of the progress or regression of the disease during the period of treatment Second, the clinical course of ocular tuberculosis in the immune-allergic rabbit is amazingly similar to the usual clinical pattern of the disease Third, it is conceivable that a therapeutic effect may be more pronounced in a small, localized focus of tuberculosis, such as a lesion in the eye, walled off by the fibrous scleral envelope, than it would be in general systemic infection or in spreading lesions

The use of "promin" in treatment of ocular tuberculosis has already been investigated by one group of authors, Steecken, Wolinsky and Heise<sup>14</sup> These workers reported on the effect of "promin" treatment on ocular tuberculosis in the guinea pig and found that the intensity of the disease in the eye was definitely less in the treated animals than in the controls, but the results were not striking

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11 Hinshaw, H C , Feldman, W H , and Pfuetze, K H Present Status of Chemotherapy in Tuberculosis, *Ann Int Med* **22** 696 (May) 1945

12 Petter, C K and Prenslau, W S Treatment of Tuberculosis with Diasone, *Am Rev Tuberc* **49** 308 (April) 1944

13 Pfuetze, K H Diasone in Treatment of Pulmonary Tuberculosis, *Dis of Chest* **11** 213 (June) 1945

14 Steecken, W , Wolinsky, E , and Heise, F H Treatment of Experimental Ocular Tuberculosis with Promin, *Am Rev Tuberc* **53** 175 (Feb ) 1946

As part of the general study of experimental ocular tuberculosis, we have undertaken an evaluation of the action of some of the antibiotic and chemotherapeutic agents on ocular tuberculosis. In a previous paper<sup>15</sup> our experiences with penicillin were reported. In this study the therapeutic possibilities of penicillin were subjected to a severe test. Normal rabbits, in which ocular tuberculosis pursues a destructive course, were used. These rabbits were treated with immense doses of penicillin over a forty-five day period. No deterrent or antibiotic effect on the ocular tuberculosis was observed.

In the present study "promin" and "promizole" were used in treatment of immune-allergic rabbits. In such animals ocular tuberculosis runs a more restrained course than it does in the normal rabbit. In fact, the course of the disease and the various lesions of the cornea, iris and ciliary body are amazingly similar to the generally recognized clinical picture. The drugs were therefore subjected to a much less severe test than they would be if normal rabbits were used.

After the original systemic inoculation, in the groin with a virulent human strain, the rabbit exhibits an insignificant lesion at the site of inoculation. Thereafter a restrained systemic disease develops characterized usually by absence of macroscopic lesions, and only by microscopic miliary lesions in the liver and spleen in a limited number of the inoculated animals. Only occasionally does an individual rabbit die with widespread visceral or pulmonary tuberculous lesions. The disease tends to be self limited, the rabbits live indefinitely, but after about three months they acquire a definite hypersensitivity to tuberculin and an increased resistance to reinoculation. The latter is so great that it takes at least fifty times as great a dose of bacilli to produce ocular lesions in these animals as is required for the normal rabbit. After this immune-allergic state is established, the eyes are inoculated in the anterior chamber with a proper dose of the same strain of human bacilli. There then occurs in the eye an immediate inflammatory reaction to the tuberculin in the inoculum. This is dependent on the already established hypersensitivity, in which the eyes participate. This immediate reaction fades within a week, and then follows an incubation period of three to six weeks, dependent on the degree of immunity resulting from the systemic inoculation and the size of the inoculating dose of bacilli. The onset of the ocular disease is characterized by small, hard tubercles on the iris and in the cornea, with a moderate inflammatory reaction. This disease usually runs a restrained course, there is little acute inflammation, gross caseation or necrosis, and rarely, if ever, does the eyeball rupture. In three to six months the ocular

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<sup>15</sup> Kennedy, J. D., Wood, A. C., and others. The Failure of Penicillin to Affect the Course of Experimental Ocular Tuberculosis, *Arch. Ophth.*, to be published.



disease burns out, leaving inactive, but more or less scarred, eyes. The use of immune-allergic rabbits as test animals therefore provides a self-limited ocular disease of three to six months' duration, during which period the course and intensity of tuberculosis in the treated and untreated controls can be compared.

#### TECHNIC

The immune-allergic rabbits were prepared by injecting in the groin of normal rabbits 0.5 cc of the paper filtrate of a six week old culture of virulent human tubercle bacilli. This inoculation was made in December 1945. By March 1946 a well marked cutaneous reaction to purified protein derivative had developed in all the rabbits. On May 13, they were inoculated in the anterior chamber of the right eye with 0.2 cc of a paper filtrate of a six week old culture of the same organism, so diluted that it contained 25 to 50 organisms per oil immersion field. Within forty-eight hours these rabbits manifested the usual reaction to the tuberculin in the inoculum, which subsided within a few days. By June 24, 21 of the rabbits so inoculated showed early signs of ocular tuberculosis. They were then divided into three groups. Group 1, consisting of 6 rabbits, were untreated and served as controls. Group 2, consisting of 7 rabbits, were treated with "promin", and group 3, consisting of 8 rabbits, were treated with "promizole". The treatment with both "promin" and "promizole" was commenced June 24 and was continued until the end of the experiment, in October.

The "promin" and "promizole" were given orally. The rabbits were fed with the usual "all-in-one" brand of rabbit pellets. The "promin" and "promizole" were sprayed over these pellets so that a 1 per cent concentration by weight of the drug was obtained in the food. A little "karo" syrup was added, and the pellets were dried. The rabbits were given all they could eat. Making allowances for wastage, it was calculated the individual rabbit consumed between 1,000 and 1,100 Gm of this mixture a week, which gave an approximate daily dose of 1.5 Gm of "promin" or "promizole" per rabbit per diem. This produced blood levels of from 1.5 to 3.7 mg per hundred cubic centimeters. The concentration of the drugs in the aqueous was slightly less than one-third that in the blood.<sup>16</sup>

The rabbits fed "promin" lost on the average about one sixth of their body weight in the first four weeks, but thereafter their weight remained stationary. The rabbits fed "promizole" showed no untoward reaction to the drug.

All rabbits, both control and treated animals, were examined once a week, and the degree of clinical ocular tuberculosis was estimated on a numerical scale, in the manner described in the previous papers of this series. The average reading of each group was plotted each week on coordinate paper, to give a comparative graph of the course of the disease in the three groups.

In October 1946, when the period of observation was completed, the animals were killed and autopsied and the affected eyes removed. The eyes of one-half the rabbits in each group were sectioned for histologic study, and the eyes of the remaining rabbits were used for transmission experiments. Under aseptic precautions, these eyes were opened, and the uveal tract was removed and ground up in a sterile mortar with sand and a little saline solution. The supernatant extract was then inoculated into the anterior chamber of normal rabbits. These rabbits were kept under observation for three months for the development of clinical ocular tuberculosis. They were then killed and the eyes sectioned for study.

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16 Determinations of the levels of "promin" and "promizole" in the blood and aqueous were made by Dr. E. K. Marshall.

## RESULTS

*Clinical Results*—The composite results are shown in figure 1, in which curve *A* represents the course of the untreated (control) rabbits, curve *B* the course of the animals treated with “promin” and curve *C* the course of the rabbits treated with “promizole.” The initial peak in all the curves after inoculation represents the reaction to the tuberculin in the inoculum, which largely faded within the first week. Treatment was started at the beginning of the sixth week, when early tubercles were present in all the inoculated eyes. From the sixth to the ninth week, there was no evident difference between the course of the disease in the untreated controls and that in the treated animals. However, at the beginning of the ninth week after inoculation, and after three weeks of treatment, the course in the controls (group 1, curve *A*) and that in the

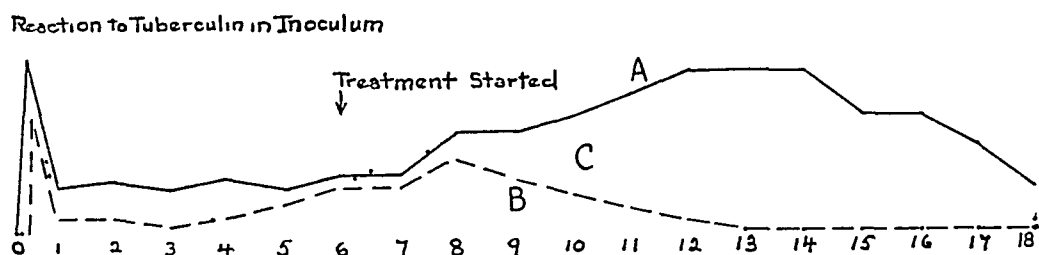


Fig 1—Clinical course of ocular tuberculosis in immune-allergic control rabbits (curve *A*), immune-allergic rabbits treated with “promizole” (curve *B*) and immune-allergic rabbits treated with “promin” (curve *C*)

treated animals (groups 2 and 3, curves *B* and *C*) showed distinct differences. The tuberculosis in the control group slowly increased, with moderate inflammatory reaction, up to the twelfth week, when it reached an average maximum of 1.1. For the next two weeks the activity in the diseased eyes remained at the same level, beginning with the fourteenth week, it slowly declined, and at the end of the eighteenth week the average activity was rated as 0.3. At the end of the experiment, of the control group, 1 rabbit showed no activity, in 2 there was only a trace, in 2 the activity was estimated at 0.5 and the remaining rabbit still had fairly well developed ocular tuberculosis, estimated at 1.0.

After three weeks of treatment with “promin” and “promizole,” the eyes of the treated rabbits began to improve slowly, and the curves for tuberculous disease in these groups began to separate from the curve for the control group. There was no appreciable difference in the curve for the group treated with “promin” and that for the group treated with “promizole.” By the twelfth week, when the disease in the control group had reached its maximum, the ocular tuberculosis in the treated rabbits was almost completely inactive. At that time 1 of the 7 rabbits treated

with "promin" showed a maximum reaction of 0.5, while the disease in the remaining 6 animals was inactive and was rated at zero. Two rabbits of the 7 treated with "promizole" showed a faint trace of activity, and the disease of 5 was entirely inactive. At the end of the fourteenth week, when the activity in the controls was still at its maximum of 1.1, all the eyes of the rabbits treated with "promin" appeared entirely quiet, with

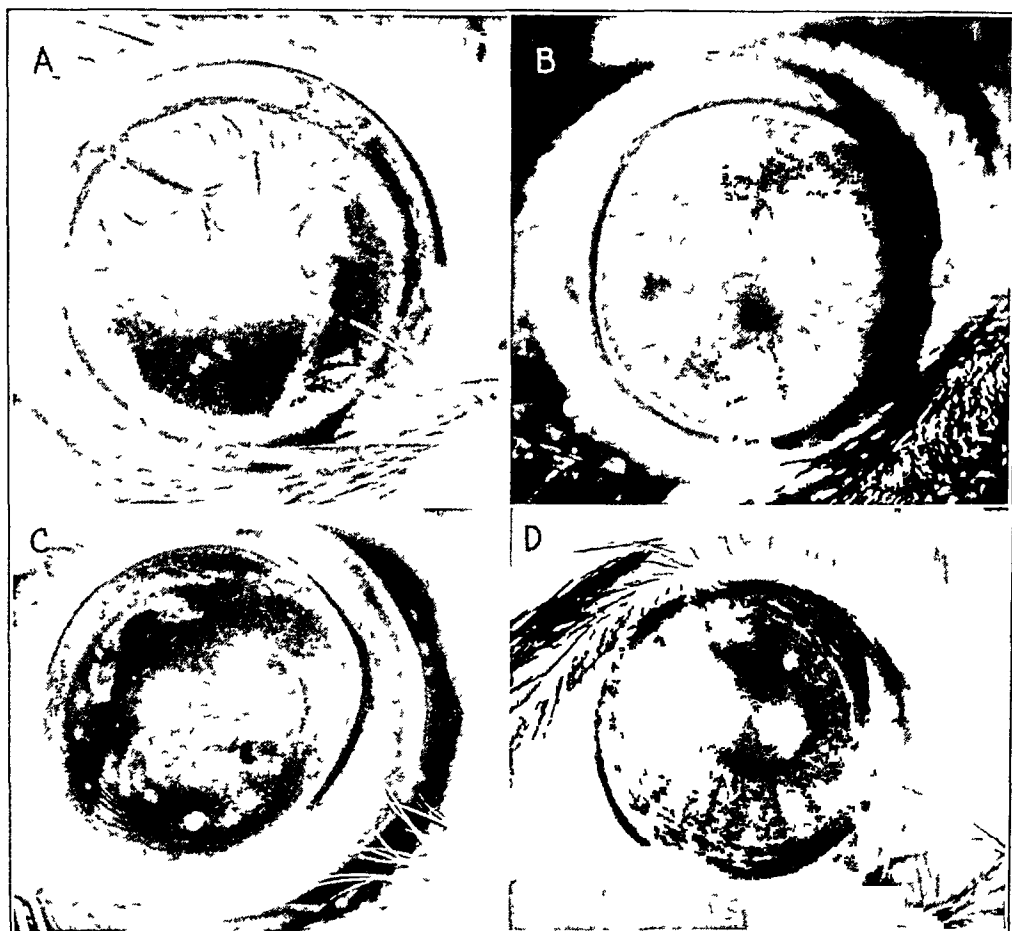


Fig 2—*A* and *B*, eyes of immune-allergic controls at end of the eighteenth week after inoculation, showing pericorneal congestion, infiltration of the cornea and corneal vascularization. Tubercles of the iris are still present.

*C*, eye of rabbit treated with "promin" at end of the eighteenth week, showing corneal scars and posterior synechiae. No activity is evident.

*D*, eye of rabbit treated with "promin" at end of the eighteenth week, showing an occasional circumscribed corneal scar and cicatrices of old tubercles in the iris. No activity is evident.

only slight residual scarring. At this time 1 of the rabbits treated with "promizole" still showed a trace of activity, while in 6 the disease was entirely quiescent. At the end of the sixteenth week all the treated eyes were entirely quiet, while 5 of the 6 control rabbits still showed active tuberculous disease of the eye, with an average activity of 0.8.

In figure 2 *A* and *B* is shown the clinical appearance of 2 of the control eyes at the end of the eighteenth week, illustrating the low grade pericorneal congestion, the corneal infiltration and the typical vascularization. Figures 2 *C* and *D* and 3*A* show the eyes of typical rabbits treated

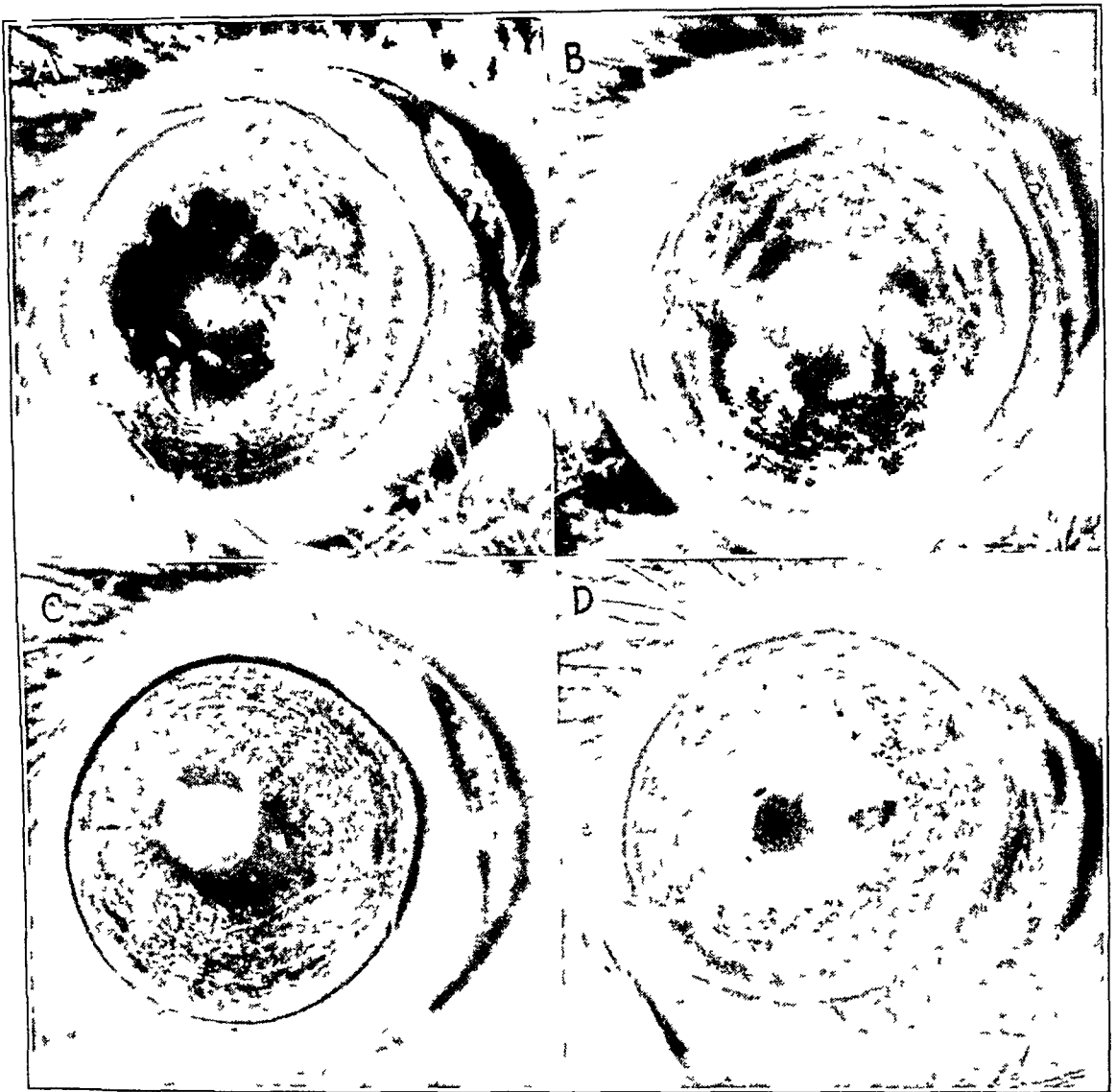


Fig 3—*A*, eye of rabbit treated with “promin” at end of the eighteenth week. The cornea is clear except for an occasional scar. There are posterior synechias and cicatrices of old tubercles in the iris, but no activity.

*B*, eye of rabbit treated with “promizole” at end of the eighteenth week, showing corneal scarring and posterior synechiae, but no activity.

*C*, rabbit treated with “promizole” at end of the eighteenth week, showing heavy central corneal scar and small cicatrices on the iris from old tubercles, with no activity.

*D*, rabbit treated with “promizole” at end of the eighteenth week, showing an entirely clear cornea (high light) and posterior synechiae in the iris, but no activity.

with “promin” at the end of the eighteenth week after inoculation. The eyes are white and free from inflammation. The corneas are clear except for the small, dense scars produced by the old lesions. The irises show some cicatricial scars and posterior synechias as residua of the former iritis, but there was no sign of any active inflammation. In figure 3*B*, *C*

and *D* are shown the eyes of typical rabbits treated with "promizole" at the end of the eighteenth week, presenting essentially the same picture as that of the rabbits treated with "promin," old scarring and no activity

*Histologic Results*—Three eyes of the control rabbits (group 1) were sectioned for study. All showed roughly the same histologic picture of numerous tubercles scattered throughout the cornea, iris and ciliary body, with little or no caseation or necrosis. Figures 4, 5 and 6 show the typical tuberculous lesions observed in an untreated immune-allergic rabbit with still active ocular tuberculosis. Figures 4 and 5 show a rather large tubercle in the cornea with epithelioid cells, giant cells and lymphocytes, but with the usual conspicuous absence of caseation. Figure 6 shows a small tubercle on the surface of the iris.

Of the rabbits treated with "promin" (group 2), the eyes of 4 were sectioned for histologic study. Two of these eyes showed no lesions of any sort other than moderate scarring of the iris (fig 7). One eye showed several small tubercles in the iris but no other lesions (fig 8). The remaining eye showed only one lesion in the sections studied—a small, healing lesion in the cornea, little more than a residual collection of lymphocytes (fig 9).

Four eyes of the rabbits treated with "promizole" were sectioned and studied. One eye showed no active lesion of any sort. The second eye showed two minor foci, one a healed lesion in the cornea (fig 10) and one an old, hard tubercle in the iris (fig 11). The third eye presented several old healing and healed tubercles in the ciliary body (fig 12), while the last eye showed scarring and thickening of the iris (fig 13) and an old healed tubercle in the cornea (fig 14). Thus, there was a definite contrast between the eyes of the control and those of the treated rabbits. In general the controls showed many more lesions, which were larger and more active than the few lesions observed in the treated animals.

*Transmission Experiments*—In the control group, the uveal tracts of 3 eyes were ground up for inoculation into the eyes of normal rabbits. All 3 transfers produced the disease, and the inoculated rabbits presented the classic picture of ocular tuberculosis in the normal rabbit, the first tubercles appearing about two weeks after inoculation and the eyes progressing to rupture by the twelfth week. Figure 15 shows the disease in 1 of these eyes at the end of the tenth week, with advanced tuberculosis of the uvea, heavy corneal infiltration and vascularization. Figure 16 presents another of these eyes, with a similar picture and beginning corneal ectasia. The histologic picture in the eyes of these transfer rabbits is illustrated in figure 17, showing a ruptured globe, and in figure 18, showing the advanced, caseating lesions of the cornea and ciliary body. These pictures, both clinical and histologic, are in sharp contrast with *A* and *B* of figure 2, which illustrate the clinical picture, and with figures 4, 5 and 6, which



Fig 4—Tubercle in the cornea of an untreated immune-allergic rabbit,  $\times 100$

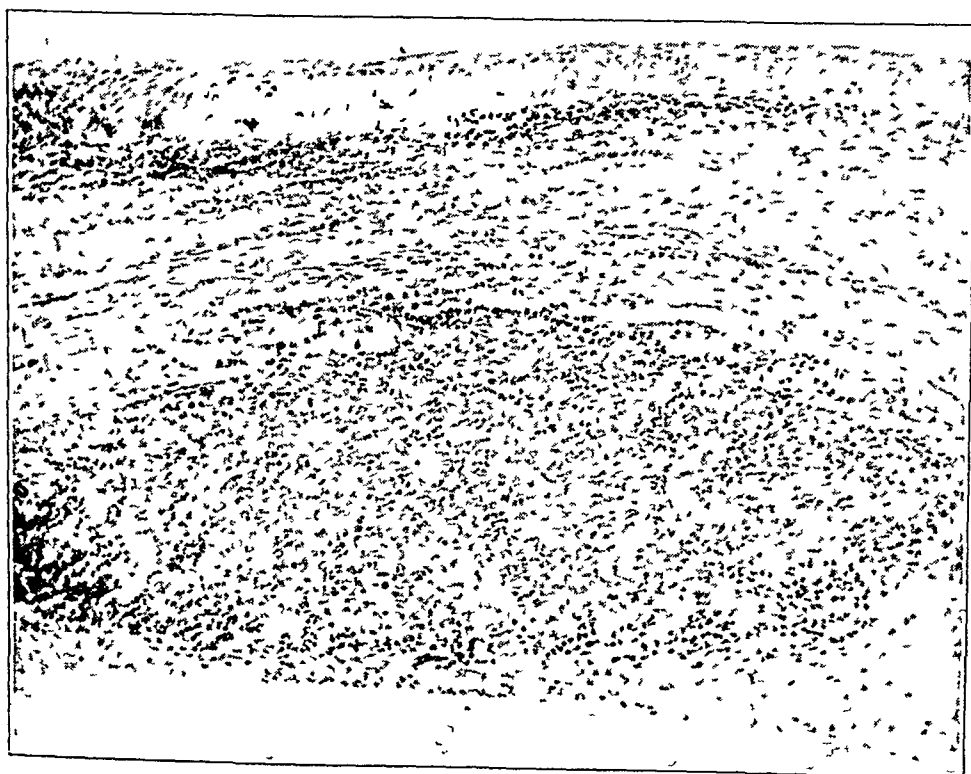


Fig 5—Tubercle in the iris of an untreated immune-allergic rabbit,  $\times 100$



Fig 6 —Tubercles at the root of the iris and in the ciliary body of an untreated immune allergic rabbit,  $\times 100$



Fig 7 —Iris of an immune-allergic rabbit treated with "promin",  $\times 100$



Fig 8—Small tubercle on the iris of an immune-allergic rabbit treated with "promin",  $\times 100$

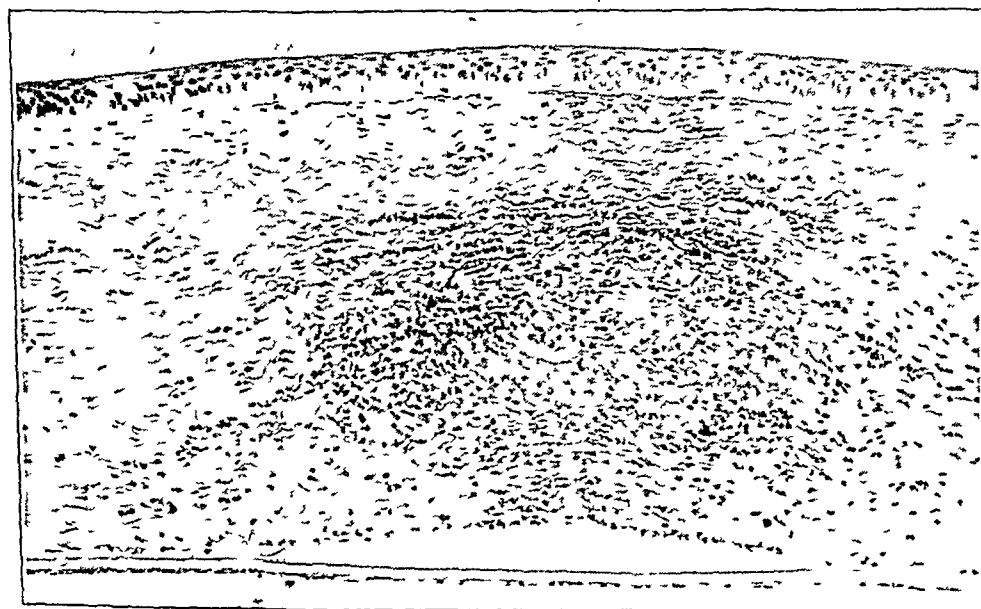


Fig 9—Tubercle of the cornea of an immune-allergic rabbit treated with "promin",  $\times 100$



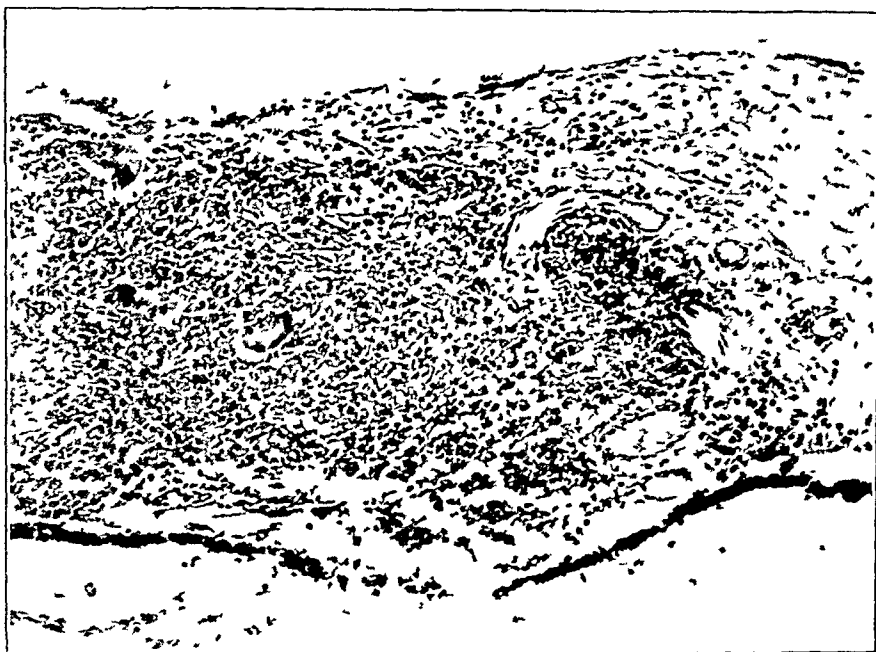


Fig 10—Healed tubercle on the cornea of an immune-allergic rabbit treated with "promizole",  $\times 100$

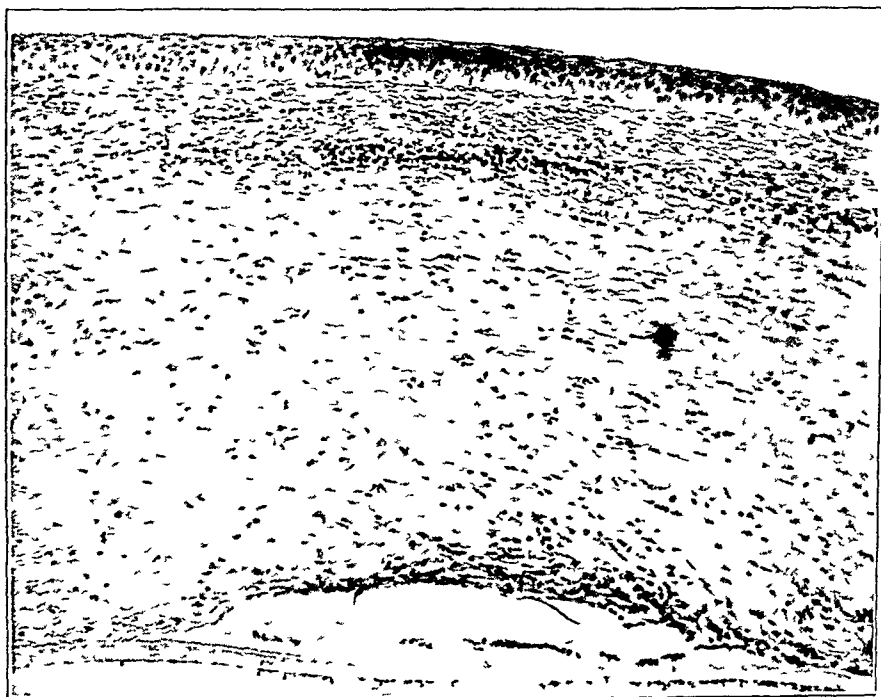


Fig 11—Tubercles in the iris of an immune-allergic rabbit treated with "promizole",  $\times 100$

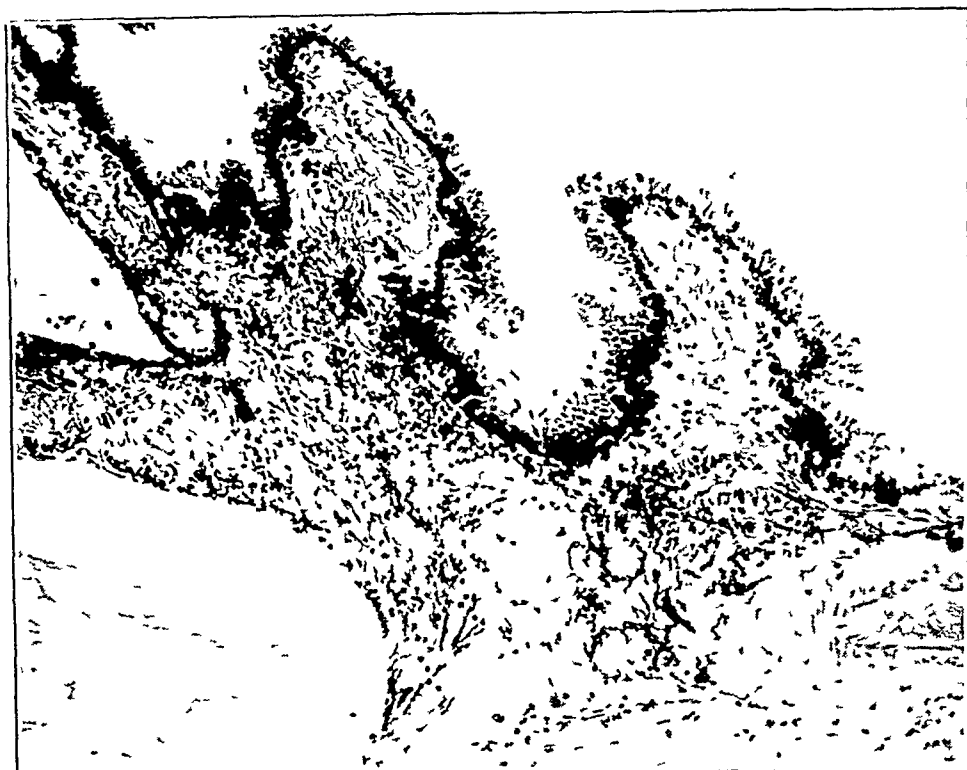


Fig 12 —Encapsulated tubercle of the ciliary body of an immune-allergic rabbit treated with "promizole",  $\times 100$

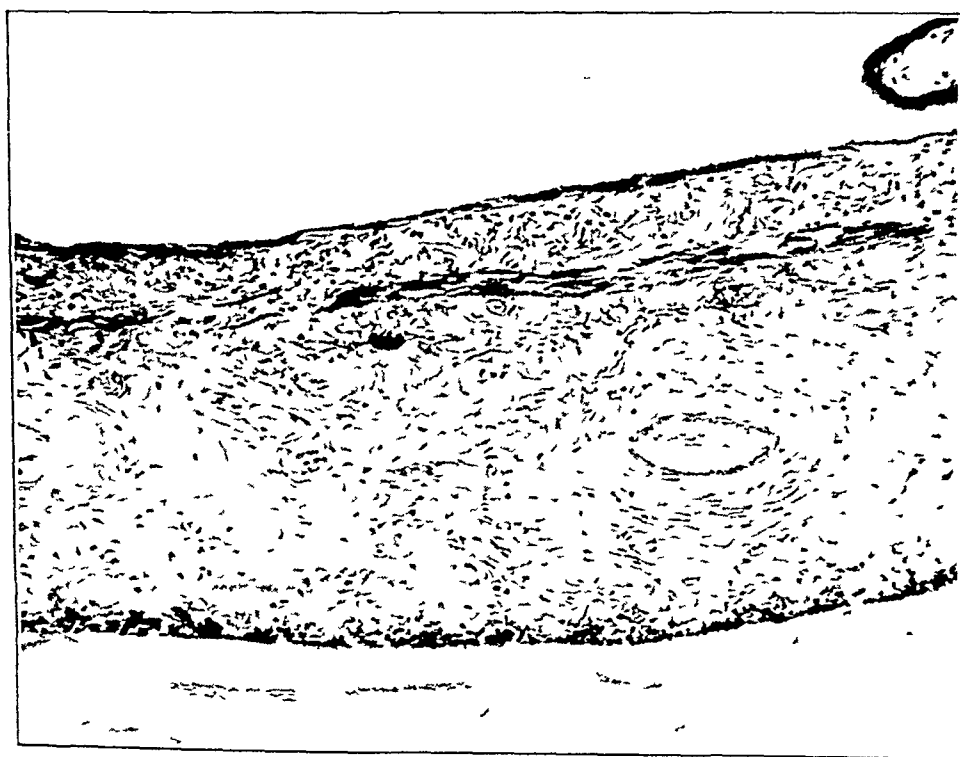


Fig 13 —Scarring of the iris in an immune-allergic rabbit treated with "promizole",  $\times 100$



Fig 14 —Healed tubercle of the cornea in an immune-allergic rabbit treated with "promizole",  $\times 100$

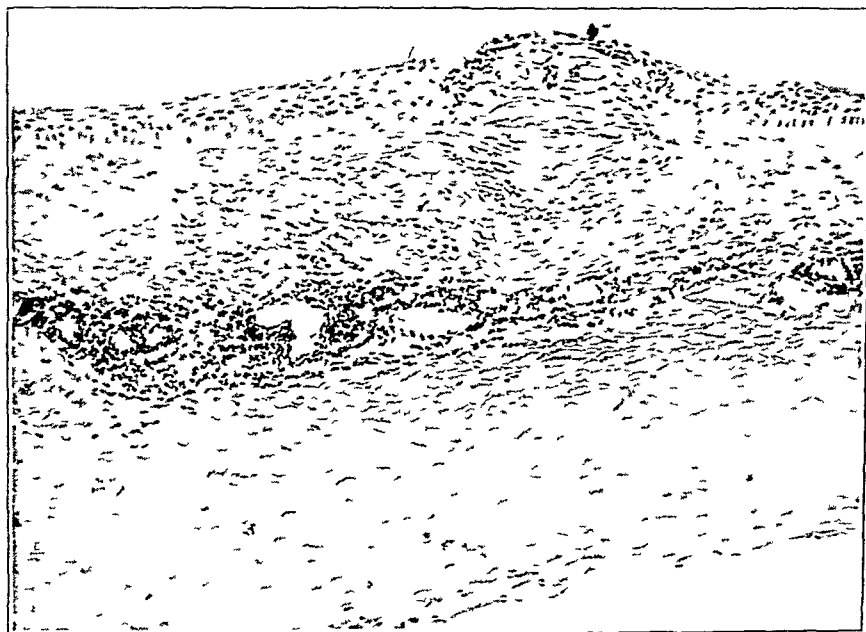


Fig 15 —Clinical appearance of a normal transfer rabbit, illustrating advanced spreading corneal infiltration blocking all view of the iris



Fig 16—Clinical appearance of a normal transfer rabbit, illustrating violent inflammatory reaction, corneal infiltration and beginning necrosis and ectasia of the cornea

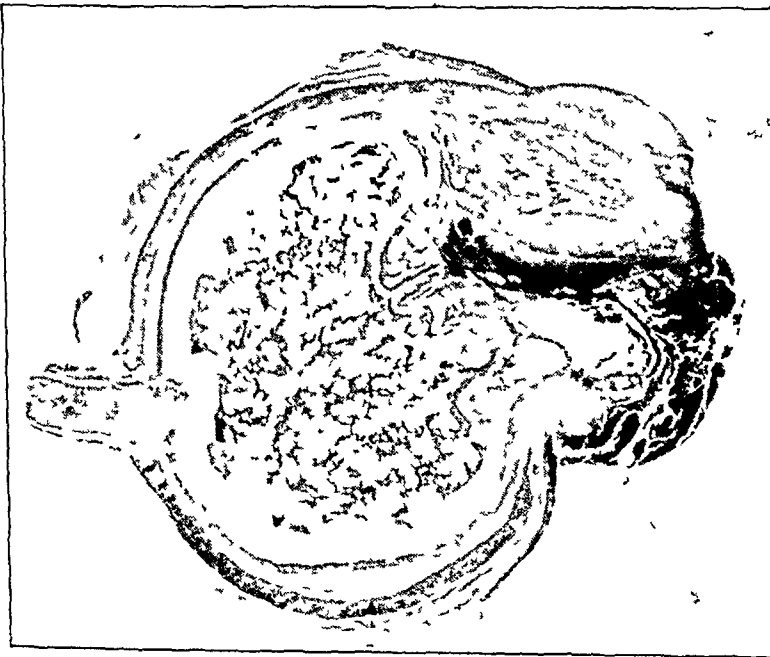


Fig 17—Ruptured globe following inoculation of a normal eye by transfer from an immune-allergic control,  $\times 100$



Fig 18—Multiple tubercles of the cornea with caseation in the cornea of a normal rabbit inoculated by transfer from an untreated immune-allergic control,  $\times 100$



Fig 19—Ciliary region of a normal rabbit eye inoculated by transfer from an untreated immune-allergic control,  $\times 100$

illustrate the histologic lesions, in the immune-allergic rabbit. They present clearly the radically different courses of ocular tuberculosis in the normal and in the immune rabbit.

Three eyes of the rabbits treated with "promin" were used for transmission studies. At the end of three months, the result of 1 of the transfers was positive and the results of 2 were negative. In the rabbit with the positive transfer there developed tubercles on the iris and infiltration and vascularization of the cornea after the long incubation period of two months, indicating that the organisms in the inoculating dose must have been either extremely scanty or of attenuated virulence. These eyes were then sectioned, and the two clinically nontuberculous eyes were likewise observed to be entirely normal on histologic study. The histologic picture of the sectioned eye of the rabbit with the positive transfer was similar to that in the eyes of the control transfer rabbits.

The extract of the uveal tract of 4 of the rabbits treated with "promizole" was injected into the anterior chambers of the eyes of normal rabbits. One of the transfer rabbits acquired a secondary infection and was discarded. At the end of three months the eyes of the remaining 3 transfer rabbits were entirely negative for tuberculosis. The animals were then killed and the inoculated eyes removed and sectioned. These eyes all showed no histologic evidence of tuberculosis.

In summary, all the eyes of the control rabbits produced tuberculous lesions on transfer. The eyes of 1 of 3 rabbits treated with "promin" produced tuberculosis on inoculation, and those of 2 did not. Three eyes of the rabbits treated with "promizole" did not produce tuberculous lesions on transfer, an additional eye being discarded on account of secondary infection.

#### COMMENT

These results require little comment. It is evident that both "promin" and "promizole" have a deterrent action on the course of ocular tuberculosis in the immune-allergic rabbit. Clinically, this deterrent action began to be manifest after three weeks of treatment, and by the fourteenth week the disease was under control and entirely quiet in the eyes of 14 of 15 treated rabbits, while the eye of the fifteenth rabbit showed only a trace of activity. The therapeutic effects of "promin" and "promizole" appeared to be about the same. "Promizole" did not produce any toxic symptoms, while some of the rabbits treated with "promin" perceptibly lost body weight. Neither "promin" nor "promizole," however, appeared to effect a complete cure of the ocular tuberculosis. Of the 7 eyes of treated rabbits sectioned for study, 5 still showed definite tuberculous lesions, although the lesions were much fewer and less severe than those shown by the eyes of the control animals. It is quite possible, even probable, that had complete serial sections been made of the 3 eyes apparently showing no

tuberculous lesions, small lesions would have been observed in these eyes

The results of the transmission experiment likewise illustrate the deterrent action of "promin" and "promizole." Whereas all the control transfer eyes produced tuberculous lesions on inoculation, only 1 of the treated transfer eyes was infective. There is nothing in this experiment that throws any light on how this lack of infectiousness was attained, whether by a bactericidal effect of the drugs on the bacteria or by an attenuation of the virulence of the organisms, allowing the preexisting immunity to become more effective.

It should be emphasized that so far this deterrent action of "promin" and "promizole" on ocular tuberculosis has been demonstrated only in the immune-allergic rabbit, in which, in addition to the chemotherapeutic effect of these sulfones, a fairly high degree of systemic immunity was also induced by the preceding systemic injection. It should be remembered that Feldman has already suggested that these sulfones may owe their deterrent action to a degradation of the virulence of the invading organisms, thus rendering the resistance of the host more effective. He did not find any evidence of increased acquired resistance developing after treatment with sulfone. In line with this suggestion, it will be interesting to see whether any deterrent action of "promin" or "promizole" against ocular tuberculosis can be demonstrated in the normal rabbit. Certainly, in this study the results may be due either to an attenuation or degradation in the virulence of the invading organism or to a specific chemotherapeutic bactericidal action.

#### SUMMARY AND CONCLUSIONS

1 Both "promin" and "promizole" exert a deterrent action on the course of ocular tuberculosis in the immune-allergic rabbit. This deterrent action becomes evident after the third week of treatment. This action of the two drugs is about the same.

2 Histologic evidences of tuberculous disease persist in the majority of the eyes of the treated animals. The lesions, however, are fewer and are less severe than in the control eyes.

3 In transfer experiments with the extract of the uveal tract from the eyes of the 7 treated animals, only 1 positive result was obtained. This occurred only after an incubation period of two months. All the control eyes gave positive transfers.

4 These results may be due either to a degradation or an attenuation of the virulence of the organisms, allowing the resistance of the host to become more effective, or to a direct bactericidal action on the bacilli.

# DACRYOCYSTITIS OF INFANCY

A Review of One Hundred Cases

J V CASSADY, M D

SOUTH BEND, IND

In the management of dacryocystitis of infancy both pediatricians and ophthalmologists have as a rule recommended conservative treatment. The teaching has been that no attempt should be made to open the nasolacrimal passages by probing the duct because early instrumentation would injure the tissues and interfere with their normal evolution. This seemed reasonable, hence, conservative treatment has been followed with but few exceptions. From a review of the literature and the present series of cases, it seems that passive treatment may at times be more harmful than early probing of the duct.

## REVIEW OF LITERATURE

There were innumerable articles during the past century warning against probing the nasolacrimal duct in cases of dacryocystitis in infancy. In 1904 Weeks<sup>1</sup> proposed probing the duct with a fairly large probe after slitting the canaliculus provided that conservative treatment was unsuccessful and nature had been given every opportunity to establish a passage. Pechin,<sup>2</sup> in 1905, in discussing dacryocystitis of infancy, expressed the opinion that it might be due to meconium in the nose which blocked the lower end of the nasolacrimal duct and that its expulsion would result in a cure. Cosmettatos,<sup>3</sup> in 1906, described five congenital anomalies of the lacrimal passages: a lacrimal cleft instead of a punctum, an extra lacrimal canal, an undeveloped lower canaliculus, absence of the lower punctum and a congenital fistula of the lacrimal sac. Zentmayer,<sup>4</sup> in 1907, advocated early dilation of the duct with probes if conservative

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1 Weeks, J E. Congenital Occlusion of the Lacrymal Canal and Acute Contagious Inflammations of the Conjunctiva in Children, *J A M A* 43:1760 (Dec 10) 1904

2 Pechin. Dacryocystite congénitale atténuée pseudo-conjonctivite des nouveau-nés d'origine lacrymale, *Arch d'opht* 25:490, 1905

3 Cosmettatos, G F. Ueber einige angeborene Anomalien der Thränenwege, *Arch f Augenh* 55:362, 1906

4 Zentmayer, W. Congenital Dacryocystitis, *Pennsylvania M J* 11:895, 1907



treatment was not successful. Two discussants (J. Ferdinand Klindinst and W. Campbell Posey) of Zentmayer's paper described such radical treatment as likely to do permanent damage by tearing or overstretching the lacrimal canal.

Edward Jackson,<sup>5</sup> in 1907, pointed out that the lacrimal secretion does not appear for several weeks after birth and that the lacrimal passages during this time may not be patulous. Since no functional call is made on the lacrimal passages, no symptoms are noted provided the opening occurs in time for the demands on it. If infection occurs, the symptoms start.

It should be remembered that the development of the lacrimal duct is a process of physiologic development and is likely to be completed at any time. We should await its completion, meanwhile controlling the inflammatory process as well as possible by palliative treatment. Conservative treatment should not be limited to a period of two to six months but as long as the symptoms are controlled by such treatment.<sup>5</sup>

Ollendorff,<sup>6</sup> in 1907, reported 7 cases of dacryocystitis of infancy in which he had been unsuccessful with conservative treatment but in which the condition promptly cleared after the duct had been probed. In 1908 Zentmayer<sup>7</sup> discussed the embryology of the nasolacrimal duct: how it arises as a thickening of epidermis along the line of the nasolacrimal groove, forming at first a ridge and later a solid cord. The cord is converted into a canal by the separation of epithelial cells. This debris of cells fills the canal with a gelatinous mass until the seventh fetal month or later. He cited possible causes of dacryocystitis of the newborn, such as (1) delayed necrosis of the cells forming the cord, (2) retention of the separated cells in the lower end of the duct, (3) obstruction due to folds of the mucous membrane in the duct and (4) partial occlusion from pressure of the turbinate bones. Zentmayer advocated probing and found that one such treatment was usually sufficient.

Kraupa,<sup>8</sup> in 1910, reported an instance of absence of the lacrimal puncta in a 14 year old boy. One eye showed complete absence of the puncta of the upper and lower lids, while the other eye showed absence of the upper lacrimal punctum.

The most valuable description of the genesis and development of the nasolacrimal passages was published in 1912 by Schaeffer.<sup>9</sup> This study

5 Jackson, E. Delayed Development of the Lacrimal-Nasal Duct, *Ophth Rec* **16** 321, 1907.

6 Ollendorff. Die Tranensackeiterung der Neugeborenen, *Ophth Klin* **11** 47, 1907.

7 Zentmayer, W. Imperforation of the Lachrymonasal Duct in the Newborn, and Its Clinical Manifestations, *J A M A* **51** 188 (July 18) 1908.

8 Kraupa, E. Die angeborene Atresie der Tränenrohrchen und ihre operative Behandlung, *Klin Monatsbl f Augenh* **48** 445, 1910.

9 Schaeffer, J. P. The Genesis and Development of the Nasolacrimal Passages in Man, *Am J Anat* **13** 1, 1912.

was made on a series of specimens representing stages from 30 day embryos to full term fetuses

The nasolacrimal duct starts from a thickening of epidermal cells in the twelve millimeter embryo which grows down into the mesenchymal tissue and detaches itself from the surface ectoderm. This epithelial cord begins to develop some lumen by the third month. Sections through one hundred day embryos show that the superior and inferior canalicular cords have extended to the free border of the eyelids and that the nasal end of the mother cord of cells has reached the nasal mucous membrane. Irregular lumens are present at various parts of the cords, more toward its extremities than at its center. The ocular end establishes a lumen long before the nasal end and the latter is delayed approximately until birth or a little later. The last portion to become patent is the site of coalescence between the nasal sprout of the mother cord and the nasal mucous membrane. The position of the ostium whether at the highest point of the inferior meatus or at some lower site on the lateral nasal wall and the shape of the ostia whether large, wide open, or more or less guarded by folds of mucosa depends upon the point and extent of coalescence between the nasal end of the mother cord and nasal mucosa.<sup>9</sup>

This exhaustive description of the genesis of the nasolacrimal duct is replete with illustrations of imperforate ducts in both 7 month and full term fetuses.

Wiener and Sauer,<sup>10</sup> in 1914, reported 2 cases in persons 50 and 70 years of age, respectively, in which an imperforate membrane obstructed the lower end of the lacrimal duct. A probe passed through the duct was located in the inferior meatus under the mucosa, and it was necessary to have the mucosa slit over the probe to establish the patency of the nasolacrimal membrane. In 1917, Roy,<sup>11</sup> in reporting on a questionnaire sent to a number of ophthalmologists asking their treatment of epiphora of the newborn, found that most of the replies favored conservative management, in the belief that the ailment commonly corrected itself with the development of the child. He advocated massage of the lacrimal sac together with use of an astringent wash for the eye, and also cleaning the nasal cavity as a routine.

Green,<sup>12</sup> in 1917, said that infantile dacryocystitis was the result of blockage of the lower end of the duct with fetal remains. He asked

What do we do if we are dealing with a hypodermic needle that has become plugged with dirt, cotton, or dried blood? We push the plugs through with a fine wire. In probing an infant's lacrimal duct we are establishing a normal function with less danger to the tissues than treatment by forceful pressure over an infant's tear sac that has already been weakened by distention and infection.

He reported 3 cases in which the condition cleared up with one probing.

<sup>10</sup> Wiener, M, and Sauer, W. E. Dacryocystitis Caused by a Membranous Closure of the Nasal Duct, *Ann Ophth* **23** 487, 1914.

<sup>11</sup> Roy, D. Lacrymal Stenosis in Infants and Its Treatment, *Charlotte M J* **75:78**, 1917.

<sup>12</sup> Green, J. Treatment of Dacryocystitis in Infants, *J Missouri M A* **14**: 427 1917.

Curdy, in discussing Green's paper, objected to probing as likely to prevent the normal development of the duct Fuchs,<sup>13</sup> in 1917, said

The upper end of the canal is the narrowest part of the duct, there is a venous plexus surrounding the nasolacrimal duct The mucosa of the duct and sac is lined with a double layer of cylindrical epithelium Mucous membrane projects in folds into the lumen of the lacrimal passages (called valves)

In Cunningham's "Anatomy,"<sup>14</sup> the nasolacrimal duct is described as about 18 mm in length, with a diameter of 3 or 4 mm, the duct being directed downward and slightly backward It opens at the junction of the anterior one fourth with the posterior three fourths of the inferior meatus of the nose

Schaeffer,<sup>15</sup> in 1920, described as very common, irregularities and diverticula of the nasolacrimal duct, with an occasional side to side union of the lacrimal sac and the nasolacrimal duct Successful probing of the duct depends on a lacrimal sac merging gradually with a nasolacrimal duct, with a fairly regular contour, otherwise artificial openings and passageways may occur with probing He described and illustrated eleven types of nasolacrimal ostiums and stated

the abutting layers of epithelium with a limited amount of intervening connective tissue may not rupture at birth or shortly after Atresia in the newborn is due to an unruptured lacrimonasal membrane, and in these surgical intervention may be necessary<sup>15</sup>

Nagel,<sup>16</sup> in 1920, finding only one reference to bilateral congenital atresia of the nasolacrimal duct in the literature up to that time, stated that it was rare He advocated conservative treatment and, if this failed, probing through the upper canaliculus into the duct McMurray,<sup>17</sup> in 1921, reported on 2 children with congenital stenosis of the nasolacrimal duct whom he treated conservatively until he considered them old enough to have the nasolacrimal ducts dilated safely (from 3 weeks until 2½ years of age) The treatment was expression of the sac, with the instillation of mild protein silver U S P Stieren and Krebs, in discussing McMurray's paper, advocated probing the duct with the patient under general anesthesia if the conservative treatment was not successful within three or four weeks Van der Hoeve,<sup>18</sup> in 1921 pointed out that amniotic

13 Fuchs, H Text-Book of Ophthalmology, edited by A Duane, ed 8, Philadelphia, J B Lippincott Company, 1917

14 Cunningham, D J Cunningham's Manual of Practical Anatomy, ed 5, New York, William Wood & Company, 1921, p 825

15 Schaeffer J P The Nasolacrimal Passageways, in The Nose and Olfactory Organ in Man, Philadelphia, P Blakiston's Son & Co, 1920, p 244

16 Nagel, C S G Congenital Atresia of the Lacrimal Duct, Am J Ophth 3 406, 1920

17 McMurray, J B Congenital Stenosis of Nasolacrimal Duct, Pennsylvania M J 25 494, 1921

18 van der Hoeve, J The Development of the Lacrymal Canal in Normal and Abnormal Conditions Tr Coll Physicians, Philadelphia 43 187, 1921

bands may form barriers to the development of the lacrimal caruncle and ducts. In 1921 Zentmayer<sup>19</sup> noted that 25 per cent of cases of dacryocystitis occurred before the tenth year and that the condition was due to an inadequately treated congenital atresia.

Kramer,<sup>20</sup> in 1922, tried to associate the etiologic factor in congenital dacryocystitis with gonorrhea in the parents. Doub and Carter,<sup>21</sup> in 1922, visualized the nasolacrimal passages roentgenographically in adults but not in children. In 1923 Crigler<sup>22</sup> advocated manual expression with pressure exerted by the thumb over the sac to force an obstructing plug from the unopened end of the duct. Meller,<sup>23</sup> 1923, advocated conservative management, but if this failed, he recommended probing of the duct, preferably with a hollow probe to which a lacrimal syringe could be attached to avoid the inconvenience of having to irrigate the sac and duct. Peters,<sup>24</sup> in 1923, in a report of cases in two families, expressed the opinion that congenital atresia of the nasolacrimal duct might be hereditary and familial.

Rollet,<sup>25</sup> in 1927, stated the opinion that treatment of congenital dacryocystitis should consist of irrigations and expression of the sac, and not of instrumentation. Arrand, in a discussion of Rollet's paper, advocated forceful irrigation of the lacrimal passages by catheterization of the duct. Coronat further observed an abscess of the sac after catheterization. Lyle,<sup>26</sup> in 1928, compared roentgenographically the nasolacrimal duct of infancy with that of an adult. Campbell and Carter,<sup>27</sup> in 1929, pointed out that "any treatment of lacrimal stenosis to be thoroughly effective, must relieve the collection of tears and pus in the patient's eyes." Meller,<sup>28</sup> in 1929, advocated expression of the sac and, if this failed, probing of

19 Zentmayer, W. Congenital Atresia of the Lacrimonasal Duct, *Tr Coll Physicians, Philadelphia* **43** 172, 1921.

20 Kramer, R. Zur Aetiologie der Dacryocystitis congenita, *Ztschr f Augenh* **49**:20, 1922.

21 Doub, H. P., and Carter, J. M. An X-Ray Demonstration of the Nasolacrimal Passageways Normal and Obstructed, *J Radiol* **3** 521, 1922.

22 Crigler, L. W. The Treatment of Congenital Dacryocystitis, *J A M A* **81** 23 (July 7) 1923.

23 Meller, J. Occlusion of the Duct in Newborn Children, in *Ophthalmic Surgery*, ed 3, Philadelphia, P. Blakiston's Son & Co., 1923, p 23.

24 Peters, R. Zur Kenntnis der Atresia ductus-nasolacrimalis congenita, *Klin Monatsbl f Augenh* **71** 726, 1923.

25 Rollett. La dacryocystite congénitale et son traitement, *Lyon méd* **139** 23, 1927.

26 Lyle, D. J. Occlusion of the Nasolacrimal Duct in the Newborn, *Arch Pediat* **45** 313, 1928.

27 Campbell, D., and Carter, J. Stenosis of the Nasolacrimal Passages, *Arch Otolaryng* **9** 367 (April) 1929.

28 Meller, J. Diseases of the Lacrymal Apparatus, *Tr Ophth Soc U Kingdom* **49** 233, 1929.

the duct, but noted that the latter might have to be followed by massage of the sac to bring it back to normal

Ferrer,<sup>29</sup> in 1930, advocated catheterization of the lacrimal passages in cases of infantile dacryocystitis as promptly as possible after a diagnosis of congenital dacryocystitis is made. He cited at length distressing sequelae of failure to establish patency of the nasolacrimal duct soon after birth. Pesme,<sup>30</sup> in 1931, recommended catheterization of the lacrimal canal as soon as possible after the child was 15 days old and deplored temporizing. Woodruff,<sup>31</sup> in 1931, reported that most of the cases of dacryocystitis of infancy come to the ophthalmologist at about 6½ months of age. A large number require no treatment other than irrigation of the lacrimal sac or, if the duct is not patent, the passing of a probe through it into the nose. Another probe was then passed under the inferior turbinate body, and the two were rubbed together in order to break through and establish a patent lumen.

Jaegers,<sup>32</sup> 1931, described a 1 day old infant with a bilateral swelling of the lacrimal sac. The swelling subsided on the fourth day on one side but required surgical drainage on the other. Majerus,<sup>33</sup> in 1931, observed a case of congenital atresia of the nasolacrimal duct of a colt, similar to that seen in dacryocystitis of the newborn, in which treatment consisted in passing a probe through the lower end of the duct. Charamis,<sup>34</sup> in 1931, described two congenital anomalies of the lacrimal passages—one, a duplicated lower lacrimal punctum that was not permeable, the other, a condition in which the duplicate puncta were both permeable and connected with the lacrimal passages.

Campbell,<sup>35</sup> in 1933, said

Tears as a rule are not shed until about three months of age. The accessory glands supply moisture to the conjunctiva and cornea in early infancy.

He suggested treatment of dacryocystitis of the newborn with instillations of silver nitrate and weak epinephrine solution. If this treatment was unsuccessful, he used repeated probings of the duct at four to seven day intervals. Duke-Elder,<sup>36</sup> in 1933, noted "that at the six centimeter

29 Ferrer, H. Dacriocistitis neonatorum, *Vida nueva* **25** 207, 1930

30 Pesme, P. La dacryocystite congénitale. Aspect clinique, diagnostic, traitement, *J de med de Bordeaux* **108** 955, 1931

31 Woodruff, H. W. Congenital Dacryocystitis, *Illinois M J* **60** 380, 1931

32 Jaegers, F. Der Reizkatarrh und die Dakryozystitis der Neugeborenen, *Ztschr f Geburtsh u Gynak* **100** 42, 1931

33 Majerus, C. J. Atresia of the Nasolacrimal Duct (in a Colt), *Vet Med* **26** 225, 1931

34 Charamis, J. S. Sur deux cas d'anomalies congenitales des voies lacrymales, *Arch d'opht* **48** 216, 1931

35 Campbell, R. A. Dacryocystitis in Infants, *Minnesota Med* **16** 267, 1933

36 Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1933, vol. 1, pp. 235 and 366

embryo stage, the lumen of the system is normally open except at the lid puncta and the inferior orifice. The former opens just before the lids separate and the latter at the eighth month.

Riser,<sup>37</sup> in 1935, reported 54 instances of dacryostenosis in children from 1 month to 12 years of age, in 7 of which the condition was bilateral. The average age at which the symptoms appeared was 1½ months. The age at which these patients were first seen by the ophthalmologist was about 6 months. Conservative therapy for two and one-half months resulted in subsidence of the symptoms in 21 cases. In 9 cases probing relieved the symptoms in about three weeks. In 50 per cent, however, relief was obtained with conservative treatment.

In 1935, Schwarz,<sup>38</sup> after examining 207 nasolacrimal ducts in fetuses ranging in age from 3 months to full term, observed atresia of the nasal ostium of the duct in one third of the specimens examined. During the last three months of fetal life the incidence of closed ostiums was practically the same, 35 per cent. The lacrimal sacs and ducts were distended, and large terminal cysts, or bullae, protruded into the inferior meatus if atresia of the nasal end of the duct existed. Fleischer (Erlangen), in commenting on Schwarz's paper, said that the majority of these closed ostiums must open up spontaneously at or soon after birth because congenital atresia of the nasolacrimal duct is rarely observed. Schwarz, in closing the discussion, said that even slight trauma, especially that incident to delivery, is capable of bursting the terminal delicate bulla in congenital atresia. This accounts for the relative infrequency of atresia in early infancy as compared with its great frequency, 35 per cent, in the antenatal material.

In 1935, Bujadoux<sup>39</sup> described a rare congenital malformation of the nasolacrimal duct which he visualized roentgenographically after filling it with a solution of eugenol and a zinc compound. Wokurek and Kraupa,<sup>40</sup> in 1936, stressed the hereditary and familial character of congenital occlusion of the nasolacrimal duct on the basis of cases that occurred in their experience. Berens,<sup>41</sup> in 1936, described the lacrimal sac and duct as forming one continuous membranous tube, the sac being

37 Riser, R. O. Dacryostenosis in Children, *Am J Ophth* **18** 1116, 1935.

38 Schwarz, M. Der angeborene Verschluss des Tranennasenganges, *Ber ü d Versamml d deutsch ophth Gesellsch* **50**:30, 1934, translated, *Arch Ophth* **13**:301 (Feb) 1935.

39 Bujadoux. Malformation congenitale du canal lacrymal. Emploi en ophtalmologie du plombage eugenol-zinc, *Bull Soc d'opht de Paris*, 1935, p. 439, *Lyon méd* **156**:238, 1935.

40 Wokurek, W., and Kraupa, E. Der angeborene Tranennasengangverschluss. *Ztschr f Augenh* **90** 273, 1936.

41 Berens, C. Congenital Atresia of the Lacrimal Duct, in *Diseases of the Eye*, Philadelphia, W. B. Saunders Company, 1936, pp. 27, 39 and 345.

flattened from side to side by the fascia or periosteum sweeping from one crest of the lacrimal fossa to the other. He advocated probing without the use of anesthesia but stated the procedure might have to be repeated several times.

Debroeu and Hermans,<sup>42</sup> in 1937, described an instance of duplicated lacrimal punctum in the lower lid of a 12 year old boy—a congenital anomaly of the lacrimal passages. Chaves Velando,<sup>43</sup> in 1937, cited the relative frequency of dacryocystitis of the newborn simulating purulent conjunctivitis. Gifford,<sup>44</sup> in 1937, said that congenital stenosis is much commoner than is generally believed. He advocated probing through the upper punctum and canaliculus (never the lower) and using a large probe, no. 10 Bowman, even in small infants.

Hardesty,<sup>45</sup> in 1938, reported the incidence of this condition in 1,538 newborn infants as 1.75 per cent. He had observed excessive lacrimation during the first two weeks of the baby's life in some instances. In 34 per cent drainage into the nose occurred during lavage, while in the remainder probing was required to establish drainage. He expressed the belief that it was necessary to clear up the infection in the sac before probing the duct.

Schaeffer,<sup>46</sup> in 1937, again pointed out that the nasolacrimal membrane often remains unruptured at birth. The nasal ostium of the duct may (1) fail of canalization, and its membrane remain intact, (2) be of microscopic size and inadequate for normal function, (3) be buried in mucosa of the lateral wall of the inferior meatus and guarded by a valve-like structure of mucous membrane, or (4) be wide open and adequate. Zentmayer,<sup>47</sup> in 1937, said that in only 1 case in his experience was more than one probing required, and he strongly urged early probing to clear up dacryocystitis of infancy. Harman,<sup>48</sup> in 1938, advocated that the punctum be dilated sufficiently to admit the nozzle of a lacrimal syringe for irrigation.

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42 Debroeu, G., and Hermans, R. *Blepharite par anomalie congenitale des voies lacrymales*, Bull. Soc. belge d'opht., 1937, no. 75, p. 109.

43 Chaves Velando, L. A. *Falsas conjunctivitis purulentas del lactante—de origen lacrimal*, Cron. med., Lima 54: 373, 1937.

44 Gifford, S. P. *Ocular Therapeutics*, Philadelphia, Lea & Febiger, 1937, p. 278.

45 Hardesty, J. F. *Obstruction of the Lacrimal Passages in the Newborn*, Am. J. Ophth. 21: 551, 1938.

46 Schaeffer, J. P. *Developmental and Anatomical Factors in Dacryocystitis*, Am. J. Ophth. 20: 1252, 1937.

47 Zentmayer, W. *Congenital Imperforations of the Nasolacrimal Duct*, Am. J. Ophth. 20: 1256, 1937.

48 Harman, N. B. *Treatment of Minor Conditions in Eye*, Brit. M. J. 1: 861, 1938.

Becker,<sup>49</sup> in 1938, described a swelling of the lacrimal sac occurring in two different infants on the second and third days after birth. This was associated with atresia of the nasolacrimal duct at its nasal opening. Even in these newborn infants the sac was observed to be filled with a clear, ropy fluid. The swelling of the sac subsided promptly after probing the duct. Larsson,<sup>50</sup> in 1938, stated that early probing after the discovery of the atresia was an excellent method of treatment and that a single probing usually sufficed. He reported 2 instances of dacryocystitis in which the patency of the duct could not be established by probing and required an intranasal resection of the end of the inferior turbinate body to expose the probe and the duct.

Granstrom,<sup>51</sup> in 1938, reviewed 640 cases of infection of the sac, 32 of which were of children under 15 years of age. In 13 of these cases the infection was probably due to congenital stenosis of the nasolacrimal duct. The same author,<sup>52</sup> in 1939, reported 28 cases of dacryocystitis in children from 1 to 15 years of age, in most of whom the condition was attributed to neglected congenital stenosis of the duct. Among the patients was a child with loss of vision from a corneal ulcer due to dacryocystitis of the newborn.

Botteri,<sup>53</sup> in 1939, urged pediatricians to differentiate dacryocystitis of infancy from conjunctivitis. He reported on 25 patients, ranging in age from 3 days to 3 months, whom he had treated by pressure over the sac in an attempt to rupture the membrane occluding the lower end of the duct. Wiener and Alvis,<sup>54</sup> in 1939, advocated dilation of the duct with a probe well lubricated with petrolatum U S P. MacGillivray,<sup>55</sup> in 1939, reported use of surgical diathermy in destruction of the sac and duct in

49 Becker, F. Zum membranösen Verschluss des oberen und unteren Endes des Tränennasenganges, *Klin Monatsbl f Augenh* **101** 569, 1938.

50 Larsson, S. Treatment of Congenital Atresia of Nasolacrimal Duct, *Acta ophth* **16** 271, 1938.

51 Granstrom, K. O. Die Dakryozystitis bei Kindern, mit besonderer Berücksichtigung vernachlässigter Fälle von kongenitaler Stenose des Ductus nasolacrimalis, *Acta ophth* **16** 512, 1938.

52 Granstrom, K. O. La dacryocystite chez les enfants, en considérant spécialement des cas négligés de sténose congénitale du conduit naso-lacrymal, *Ann d'ocul* **176** 836, 1939.

53 Botteri, A. Ueber die eitrige Entzündung des Tränensackes bei Neugeborenen, *Ann pædiat* **154** 236, 1939, Purulent Dacryocystitis in Newborn, *Liljecvjes* **61** 277, 1939.

54 Wiener, M., and Alvis, B. Y. Epiphora of Newborn, in *Surgery of the Eye*, Philadelphia, W. B. Saunders Company, 1939, p. 405.

55 MacGillivray, A. M. Infantile Dacryocystitis Treated by Surgical Diathermy, *Brit J Ophth* **23**:630, 1939.



several infants with dacryocystitis of the newborn Busacca,<sup>56</sup> in 1940, advocated the use of Besredka filtrates for irrigating the nasolacrimal duct and sac About 2 cc of bouillon containing the Besredka filtrate was used for irrigation every other day until the purulent secretion diminished

Velez,<sup>57</sup> in 1941, expressed belief that most cases of dacryocystitis occurred in newborn infants with flat noses Owing to the improper bony development of the nose, catheterization of the lacrimal canal should not be carried out, but, rather, massage, lavage and general tonic treatment should be used until bony development progresses Traquair,<sup>58</sup> in 1941, said that the congenital form may be present in several children of the same family Inheritance from parents who have the adult form is interesting, but its significance is not clear The congenital form can be easily cured by one passage of a probe or by repeated expressions The upper punctum was used for probing

Meek<sup>59</sup> in 1941, said that "if one waits long enough in almost every case, the tearing will clear up, but if one has used conservative treatment until the child is seven months old, one should then probe the duct" He suggested that if constant tearing persists in a baby even after probing, the cause may be tuberculosis, and it is best treated with roentgen radiation Walker,<sup>60</sup> in 1941, advocated slitting the upper canaliculus and passing a probe with the patient under general anesthesia Fourteen infants with this condition were reported in which one such probing permanently relieved the epiphora Hardesty,<sup>61</sup> in 1941, emphasized irrigation of the sac sufficiently with a large-tipped syringe to clear up the infection before probing was done In some instances it was necessary to slit the canaliculus sufficiently to insert a Ewing syringe of the large dropper type if the pus was thick

Judge,<sup>62</sup> in 1941, stated that the imperforate ostium was due to a collection of detritus at the lower end of the lacrimal duct, lying either inside or outside the nasal aperture obstructing the lumen In some cases

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56 Busacca, A Simple Method of Treating Dacryocystitis in Newborn, *Arch Ophth* **24** 1256 (Dec) 1940

57 Velez, D M Lagrimeo en los niños de pecho por falta de desarrollo de los huesos propios de la nariz, *An Soc mex de oftal y oto-rino-laring* **16** 317, 1941

58 Traquair, H M Chronic Dacryocystitis, *Arch Ophth* **26** 165 (Sept) 1941

59 Meek, R E Applied Anatomy of the Eye, *Arch Ophth* **26** 495 (Sept) 1941

60 Walker, J D Nasolacrimal Stenosis, *Texas State J Med* **37** 544, 1941

61 Hardesty, J F Obstruction of Lacrimal Passages in Newborn Infant, *J. Missouri M A* **38** 40, 1941

62 Judge, H V Dacryocystitis of Newborn, *New York State J Med* **41** 25, 1941

the condition would cure itself spontaneously by sneezing or aspiration. He advocated passage of a small nasal applicator tightly wound with cotton along the under surface of the inferior turbinate body to dislodge a mass of mucous and epithelial cells blocking the duct. "Probing could be avoided in fifty per cent of the cases, twenty-five per cent responding to the nasal approach and the other twenty-five per cent to expression."

Moret and associates,<sup>63</sup> in 1942, reported 14 cases of dacryocystitis of infancy in which irrigation of the sac with saline solution under pressure was used, but some of the ducts had to be catheterized. Naugle,<sup>64</sup> in 1943, reported 4 cases of infantile dacryocystitis, in 2 of which cure had been effected by irrigations with solution of sodium sulfathiazole. Goar,<sup>65</sup> in 1943, advised probing the duct if conservative treatment or lavage of the sac was not successful in clearing the dacryocystitis of the newborn.

In 1945, Arruga<sup>66</sup> reported a case of dacryocystitis of the newborn successfully treated by irrigations of solution of penicillin and probing the duct. Simpson,<sup>67</sup> in 1945, said that it is well known that digital expression of the sac and probing when indicated leads to cure and recovery in the vast majority of cases. He suggested that, in addition to obstruction by an epithelial plug, infection may form a mucoid plug, which may be removed by digital pressure or syringing. Oral chemotherapy (sulfadiazine) was used, together with manual expression of the sac, with recovery in 2 cases.

Gifford,<sup>68</sup> in 1946, suggested that the condition could be familial and hereditary and said that probing the lacrimal passages may be used to cure the mucocele in infants, but only as a last resort, and not until the child is 6 to 9 months old. Too early probing or the use of large instruments may lead to permanent strictures and serious later complication.

#### PRESENT STUDY

One hundred cases of dacryocystitis in infancy which I have treated during the past few years have been reviewed as to age, sex, side affected, symptoms, type and duration of treatment, complications and end results.

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63 Moret, R. L., Damianovich, J., and Freyre, A. V. Obstruction, Causing Conjunctivitis of Infants, *Semana med* 1:419, 1942.

64 Naugle, T. C. Treatment of Dacryocystitis in Children. Effects of Sulfathiazole, Sulfonamide, *Mississippi Doctor* 20:411, 1943.

65 Goar, E. L. Infantile Dacryostenosis, *M. Rec. & Ann.* 37:611, 1943.

66 Arruga, H. La penicilina en un caso de dacriocistitis congenita grave, *Arch. Soc. oftal. hispano-am.* 5:133, 1945.

67 Simpson, G. V. Sulfadiazine (Sulfonamide) in Treatment of Dacryocystitis of Newborn, *Arch. Ophth.* 33:62 (Jan.) 1945.

68 Gifford, H. Surgery of the Lacrimal Apparatus, *American Academy Ophthalmology, Graduate Lecture Brochure*, 1946, course no. 229.

This study has led to the conclusion that the cause of dacryocystitis of the newborn is congenital atresia of the lacrimal duct and that this anomaly should be corrected as early as possible. Conservative symptomatic treatment, instead of early probing of the duct, caused distention, prolonged unnecessary inconvenience, damage and at times permanent injury to the lacrimal passages.

The onset of symptoms, watering of or mucous secretion in the eye was noted in most instances (85 per cent of cases) on the day that the child was brought home from the hospital. This was usually the ninth or tenth day post partum. Whether this was actually the date of onset, or whether the condition may have antedated the tenth day, I am trying to determine by means of an examination made by the hospital nurses in charge of the nursery. So far, in spite of examination by pressure over the lacrimal sac with a cotton-tipped applicator, only a rare case of dacryocystitis among the hospital's newborn infants has been found. The first care of the eyes evolves on the mother on the day that she brings the child home from the hospital, and her thorough examination and search for defects may account for the large number of cases noted on this day. The baby's first contact with outside cold air, when taken from the nursery and exposed, may be the inciting factor in the tearing and may account for the onset of the dacryocystitis on the day that the infant is brought from the hospital. In the other 15 per cent in whom symptoms appeared later, from several weeks to eighteen months after birth, various factors may be involved. The average age of appearance of tears is about 1 month, hence, the symptoms do not appear in some babies until nature discovers that the lacrimal duct is not patent. The instances in which the symptoms, watering and pus from the lacrimal sac, have not appeared until later, from two to eighteen months after birth, may be due to an inadequate ostium together with a superimposed infection of the sac, which has increased the obstruction. Schaeffer demonstrated such ostiums, small, shallow and slanting, in nasolacrimal ducts running beneath the nasal mucosa, with folds and valves obstructing them. In such instances the duct may be patent enough until swelling of the nasal mucosa or venous plexus obstructs it during an allergic episode or an attack of coryza.

The 100 babies with dacryocystitis in my series were almost equally divided as to sex. Heredity or a familial influence was not a factor that could be said to have a bearing on the incidence of this malady. Neither the parents nor their near relatives had a history of dacryocystitis. There were no two children of the same or of related families in the series. Heredity and a familial tendency were inquired into in order to substantiate or to disprove one of the etiologic theories suggested by several authors (Traquair,<sup>58</sup> Kraupa,<sup>8</sup> Gifford<sup>68</sup> and Peters<sup>24</sup>).

In this series of cases, the dacryocystitis occurred in 43 on the left side, in 43 on the right side and in 14 bilaterally. In the development of the nasolacrimal duct, there is, of course, symmetric growth of each side of the embryo, and the junction of the lower end of the duct with the nasal mucosa is probably effected simultaneously in the two ducts. The formation of the opening of the ostium into the nose may not occur in a high percentage of newborn infants until rupture of a membrane at the lower end of the duct occurs to establish patency of the duct. It is probable that on one side the membrane would rupture before the other or that the child might be born with both ostiums unruptured.

The average age at which these infants appeared in the ophthalmologist's office for treatment was 3 months. The ducts of 9 infants were probed during the first month of life, those of 19 others by the eighth week and those of 5 others by the eleventh week. The ducts of 13 more were probed during the third month, or a total of 46 per cent of the infants were seen by the third month. As pediatricians have realized that dacryocystitis in infancy can be cured so easily, they have not prolonged conservative treatment unnecessarily, but have sent the baby earlier to the ophthalmologist. I still find an occasional child who has had purulent dacryocystitis for seven to twelve months because the parents have been warned against probing the duct until the child is at least 6 months of age or older (case 59).

The symptoms that the child presents are tearing with mucous or purulent secretion in the eye. The conjunctiva is usually not inflamed, neither is there conjunctival or ciliary injection. Pressure over the lacrimal sac may cause an outpouring of mucous or purulent secretion into the inner canthus of the eye. The sac may be palpably or visibly distended. It refills and can be evacuated into the conjunctival sac several times a day. An attempt to wash the sac with a lacrimal syringe and cannula results in regurgitation into the inner canthus of the eye, while none of the solution goes through into the nose. Ordinarily, there is no redness or inflammatory swelling of the sac. Acute inflammation of the sac is usually secondary to chronic inflammation. In acute dacryocystitis, inflammatory symptoms are usually severe, with redness and swelling over the region of the sac, often so severe as to resemble erysipelas of the face. It is interesting that of this series of 100 cases of chronic dacryocystitis treated by probing, which theoretically should have incited an acute dacryocystitis at least in some instances, dacryocystitis occurred in only 2 (cases 1 and 57), and in both the abscess had antedated the probing.

A review of these cases of dacryocystitis of infancy reveals that in most of them there had been previous lavage, massage, attempts at expression by force and instillations of antiseptic drops. Several infants

had had chemotherapy, and some had had penicillin to clear up the dacryocystitis before they were brought to an ophthalmologist. The treatment used for all these babies at their first visit consisted in probing the nasolacrimal duct in order to establish its patency and irrigating the duct into the nose. Anesthesia was not used except in a few instances in which the size of the child or the apprehension of the parents, the referring physician or the infant seemed to make its use imperative. The success of the treatment depended in part on immobilizing the child so securely that the head could not be moved while the duct was being probed.

It is probably superfluous to describe the swathing, but immobility is such an essential part of the treatment that its explanation is too important to be omitted. The child is placed on a sheet, folded to a size of about 3 by 5 feet (9 by 152 cm). The arms extended at the child's sides are secured by wrapping first one end of the sheet over the front and tucking it under the back, then the other end of the sheet is brought over the front of the already wrapped bundle and under the back. The sheet is drawn securely tight around the extended legs and knees to prevent kicking or use of the legs or feet and to bind the legs together. The nurse now leans over the right side of the infant, holding the shoulders down with her forearms, while the head is held in her two hands to prevent its wiggling. With the illumination above and behind, the operator sits at the head of the child looking down into the lower lacrimal punctum. A 2 cc syringe containing isotonic solution of sodium chloride and fitted with a no. 23 gage, 1 inch (2.5 cm) lacrimal cannula is introduced into the lower punctum after slight dilation with a punctum dilator. As soon as the cannula engages the punctum, it is turned horizontally and slipped through the lower canaliculus until it strikes the bony wall of the lacrimal fossa. As the tip is held firmly against the osseous wall, the syringe is turned vertically and the cannula is directed almost vertically downward in the direction of the nasolacrimal groove. The cannula slides easily into the duct and downward until it pierces the lower end of the canal and its tip rests on the floor of the nose. Some of the solution may be ejected from the syringe into the sac to irrigate it as the cannula enters the sac. As soon as the cannula enters the inferior meatus, having penetrated the lower end of the occluded duct, some solution is injected to insure that the duct is now patent. The infant usually swallows or coughs, indicating that the solution is running into the throat and that the duct is unclogged. The cannula, attached to the syringe, is used instead of the solid Bowman probe so that the entire procedure, the irrigation and the probing, can be carried out with one instrumentation of the duct. A larger probe than the no. 23 gage cannula has not usually been found necessary. A solution of penicillin is used for instillation at home until the child is returned for a subsequent visit, five to seven days later. The symptoms, the mucus

in the sac and the watering of the eye, usually disappear within a few days after probing. If at the next visit the sac still contains pus, it is irrigated again by the same method, and if the duct is not yet patent it is again probed to reopen the closed aperture. It is at times found closed, and cannot be irrigated with the solution until the canal is again probed into the nose.

No. of Cases	<i>Duration of Treatment</i>	
	Length of Treatment	Average Age at First Visit, Mo
1	6 mo	11
1	4 mo	5½
4	4 wk	4½
12	3 wk	5 2
5	2 wk	8
10	1 wk	6
67	A few days	3

In an analysis of the reason that these obstructions did not always clear up promptly after probing, it is necessary to review some cases separately. In case 21, the baby, 11 months old, had had purulent right dacryocystitis since the age of 2 months. After the duct was probed, the parents, although advised to return with him in one week, did not do so until two and one-half months later, the sac, still distended with mucopurulent secretion, was washed and the patency of the duct re-established. The parents were uncooperative and difficult to manage and brought the child only irregularly for six months.

In case 73, the child, 5½ months old, had had an infection of the tear sac of the right eye since his tenth day of life, with a great deal of thick discharge. Improvement followed the first treatment, but he was not brought back for seven weeks. As so often happens when the infection of the sac smolders along, it becomes much more difficult to cure. Treatment with sulfonamide drugs, together with expression of the sac, irrigation of the eye and instillation of antiseptic drops twice a day, as well as weekly or biweekly irrigations of the sac, was carried out for two months. The duct was patent, but the sac had no tonicity and remained flabby, distended and infected. It finally cleared up four months after the first visit and remained clear.

The older age of some of the children, as well as the failure of the parents to follow through with treatment after the patency of the duct is established, are both factors in their prolonged symptoms. When the sac has been distended for several months with a mucopurulent infection, its walls are weakened, its tonicity is diminished and its recuperative ability is impaired. In order to clear up the dacryocystitis, it is necessary not only to probe the duct to insure its patency, but to treat the lacrimal sac, relieve the congestion and be sure that the patent duct functions. The follow-up treatment, that is, on the second visit soon after the duct is probed, is just as necessary as the original probing, to assure the adequacy of the lumen.

In 67 cases the symptoms disappeared promptly after a single probing, and in another 10 cases they lasted only one week. Considering that the dacryocystitis had existed in most instances since the child was 10 days old and the average age at which the infant was brought for treatment was 3 months, the lacrimal sacs had good recuperative ability. Before the ducts were probed, the infants had had symptomatic treatment since their disease had started, but this had been ineffective. The infants who were treated by probing within the first two months of life were almost without exception cured promptly by a single probing. It is possible that the dacryocystitis might have subsided spontaneously, as the advocates of conservative treatment will rightly point out, if time had been given the structures to develop normally. On the other hand, the prolonged irrigation and massage in some of the older groups would indicate that radical, early treatment may be the most conservative type of therapy.

Some of the complications are of interest and value to consider. Acute dacryocystitis, as has previously been mentioned, was observed in 2 infants, but in both before probing was used. After surgical drainage or rupture of the distended sac, the dacryocystitis was later successfully treated by probing. Eczema of the eyelid occurred once. Mild recurrence of the symptoms during acute coryza or allergic rhinitis was occasionally observed, but in these cases the duct was found to be patent to irrigation. In 1 instance (case 49) a false passage was made by the lacrimal cannula, and edema of the tissues of the lower lid occurred when the saline solution was injected. The cannula was withdrawn and reinserted into the upper punctum and canaliculus. One extra washing a week later was required, but there were no untoward symptoms from the false passage, and the dacryocystitis had entirely cleared up within fifteen days. In case 45 the duct was repeatedly blocked on three successive weekly irrigations. The fluid could be forced into the nose only after the cannula would puncture the nasal end of the lacrimal duct into the inferior meatus. This must have been due either to rehealing of the ruptured membrane of the ostium or to a submucous type of duct, with a very small ostium.

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In reviewing the subject of dacryocystitis of infancy, the embryonic development of the nasolacrimal duct is the most important factor in the causation of the disease. The development of the duct from the epithelial cordlike thickening of epidermis along the line of the naso-optic groove, its growth into the mesenchymal tissue, its detachment from the surface ectoderm, its canalization, the formation of lid and nasal sprouts of the mother cord, their contact between the eyelids and the nasal mucosa, the formation or lack of formation of the ostiums, all have been described in the literature cited. The nasal ostium of the nasolacrimal duct may not be

patent in a large percentage of newborn infants. There is a membrane over the lower end of this duct which is said to open at birth. The incidence of dacryocystitis of the newborn depends on the patency of this ostium, and in cases in which it is not patent symptoms of tearing and mucus in the infants' eye appear at about the time that the child is brought home from the hospital. Conservative treatment is probably effective in some instances, or at least at times the duct opens spontaneously, without probing. If the symptoms persist until the third month, the child is usually brought to an ophthalmologist for treatment.

The treatment advocated is probing of the nasolacrimal duct to establish the patency of its nasal ostium, followed by irrigation of the sac and duct. Prolonged conservative treatment, which has been advocated by many earlier and some later authors, is a nuisance to both the parents and the child, and is likely to result in prolonged and permanent injury to the lacrimal passages. It is not necessary to use large probes to establish the patency of the duct, one need only to insure a lumen by perforating the membrane at the nasal ostium. In the cases of dacryocystitis in which early probing was used recovery was prompt, and no untoward results of injury were experienced. In the American or the foreign literature I could find expressed only fears as to what might happen with early probing, and no evidence to substantiate the belief that injury resulted from early instrumentation. In my own cases, and in those of the ophthalmic literature, probing the duct (like pushing a stylet through an obstructed hypodermic needle) cleared the dacryocystitis in most instances with a single probing.

Several questions, however, remain to be answered. At what age do tears first start? Why does dacryocystitis of the newborn seem to start on the first day that the child comes home from the hospital? What percentage of newborn infants have an open nasolacrimal duct at birth? What is the incidence of dacryocystitis of infancy? Why does mucus distend the sac within a few days after birth in some cases? When the nasal ostium is not patent, why is the nasolacrimal duct distended in still-born or in mature fetuses?

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# SPECTRAL TRANSMISSION OF THE EYE TO ULTRAVIOLET RADIATIONS

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Quantitative determinations of the absorption of ultraviolet radiations by different structures of the eye are of importance, since various pathologic conditions, such as cataract,<sup>1</sup> retinal damage<sup>2</sup> and functional visual disturbances,<sup>3</sup> have been variously ascribed to these radiations. The measurements of absorption of ultraviolet radiations by ocular media made heretofore have been limited to photographing narrow bands of radiations transmitted through the eye. As pointed out by the author of one of these papers,<sup>4</sup> the data obtained by this means are qualitative, since it is difficult to estimate the proportion of the radiations which is transmitted through the ocular structures. In the present study quantitative information was obtained by measuring photoelectrically the fraction of radiation which was transmitted.

## MATERIALS AND METHODS

All the measurements were made on the eyes of young adult albino rabbits, weighing approximately 2 Kg. Technics used in determining the absorption of ultraviolet radiations for the different portions of the eye follow.

*Corneal Epithelium*—The epithelium was removed as a continuous sheet by gently teasing it loose from the stroma with a scalpel while simultaneously directing a fine stream of water under the surface of the loosened edge. Extreme care had to be taken to avoid tearing the epithelium, and many failures were encountered before an

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From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1 Burge, W. E. The Production of Cataract, *Arch Ophth* **47** 12 (Jan) 1918.

2 Birch-Hirschfeld, A. Die Wirkung der ultra-violetten Strahlen auf das Auge, *Arch f Ophth* **58** 469, 1904. Duke-Elder, W. S. A Histological Study on the Action of Short-Waved Light upon the Eye, with a Note on "Inclusion Bodies," *Brit J Ophth* **13** 1, 1929.

3 Wolf, E. Effects of Exposure to Ultra-Violet Light on Subsequent Dark Adaptation, *Proc Nat Acad Sc* **31** 349, 1945.

4 Graham, W. P. The Absorption of the Eye for Ultraviolet Radiations, *Am J Physiol Optics* **4** 152, 1923.

intact sheet of epithelium was obtained. To avoid tearing consequent on the use of forceps, the separated epithelium was floated in water and, while still immersed, was placed between two thin quartz cover slips.

The epithelium was relatively clear, although some swelling may have occurred as a result of the use of water in removing the tissue.

*Whole Cornea*—The cornea was removed from the eye and placed between two polished plates of quartz, the surfaces of which were ground to match the curvature of its inner and outer surfaces<sup>5</sup>.

*Aqueous and Vitreous Humors*—These fluids were taken from a rabbit freshly killed and were placed in quartz microcells of a size to give an optical path of 1 cm. The absorption data for the aqueous humor were recalculated to correspond to the thickness found in the rabbit eye, i.e., 3.2 mm. Since the thickness of the vitreous humor in the rabbit is approximately 1 cm, the data obtained with this medium did not have to be recalculated. With both media the results were adjusted to take into account the loss of about 10 per cent due to the reflecting surfaces of the container.

*Lens*—The lens, with the capsule intact, was carefully removed and placed in a specially constructed lucite chamber to hold it immobile. Quartz cover slips were held lightly against the anterior and posterior surfaces of the lens to prevent a focusing action. The lenses weighed approximately 300 mg. each.

*Whole Eye*—A chamber of design similar to that used for the lens measurements was made to hold the whole eye. A hole approximately 3 mm. in diameter was cut through the coverings in the back of the eye, and a plain surface quartz cover slip was held against the posterior portion of the eye to prevent loss of vitreous. The radiations traversed the eye in a posteroanterior direction. No quartz cover slip was used on the anterior surface of the eye.

The measurements of absorption of ultraviolet radiations were made with a Beckman spectrophotometer. In order that the beam of radiations should be smaller than the opening cut through the back of the eye, and also smaller than the pupil, a penny in which a 1.3 mm. hole had been drilled was inserted just beyond the exit slit of the instrument. This modification was also employed in using the microcells for determining the absorption of the aqueous and vitreous humors.

The exit slit of the spectrometer was set at 2 mm. The width of the wave band at 400 millimicrons was approximately 10 millimicrons, and that at 250 millimicrons, 2.3 millimicrons.

To prevent leakage of vitreous humor in making the absorption measurements for the whole eye, the spectrophotometer was turned on end. In all instances the sample to be measured was fastened to the sliding mechanism used ordinarily to contain the absorption cells. The sample could thus be moved into and out of the path of radiations in the usual manner.

## RESULTS

The per cent of absorption of various wavelengths of radiant energy by the corneal epithelium, cornea, ocular media and the whole eye is shown in figure 1. The curves show that all but approximately 1 per cent of the ultraviolet radiations of wavelengths shorter than 350 millimicrons

<sup>5</sup> The quartz plates were obtained from A. D. Jones Optical Works, Cambridge, Mass.

are absorbed by the whole rabbit eye and that the lens is chiefly responsible for this absorption. The cornea and aqueous and vitreous humors absorb most of the radiations of wavelengths shorter than 300 millimicrons,

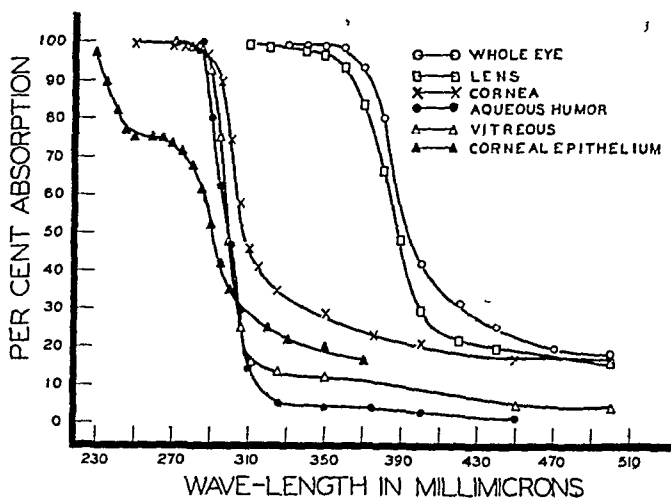


Fig 1—Percentage of absorption of ultraviolet radiations by various constituents of the eye

i.e., the abiotic portion of the ultraviolet spectrum. The corneal epithelium absorbs chiefly radiations of wavelengths shorter than 290 millimicrons.

In figure 2 the proportion of the total radiant energy incident on the outside of the eye which reaches the anterior surface of the various ocular

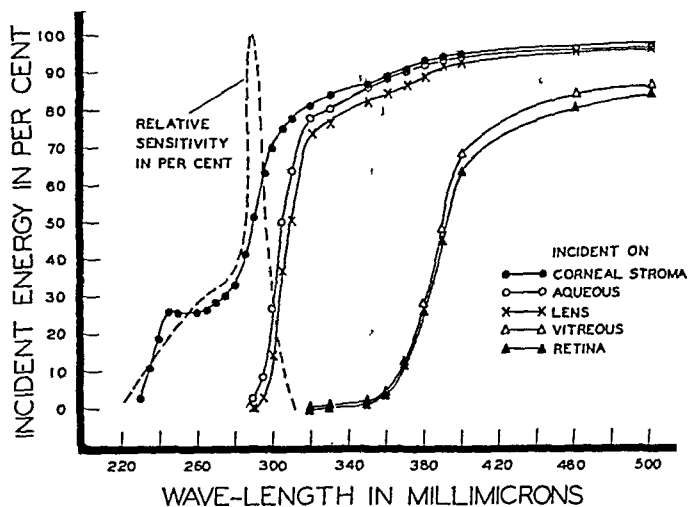


Fig 2—Percentage of ultraviolet energy incident on the outside of the eye which reaches the anterior surface of the various ocular media, plotted as a function of the wavelength

media is shown plotted as a function of wavelength. (The exact values are given in table 1.) For purposes of comparison, a curve (broken line) showing the relative sensitivity of the cornea to radiant energy of various

wavelengths is also shown in figure 2. The series of curves shows the progressive decrease with shorter wavelengths in the amount of radiant energy reaching the various interior portions of the eye. It will be seen, for example, that the ocular tissues in front of the retina absorb essentially all of the radiations producing abiotic effects, i.e., those of wavelengths shorter than 310 millimicrons, and that only a small proportion of the radiations in this region reach the anterior surface of the lens.

## COMMENT

The correspondence of the absorption peak, observed for corneal epithelium (265 millimicrons, fig. 1) with that for nucleoprotein suggests that this substance is chiefly responsible for the absorption of ultraviolet

TABLE 1—*Percentage of Energy Incident on the Corneal Epithelium Which Impinges on the Anterior Surface of the Various Ocular Media*

Wavelength Millimicrons	Corneal Stroma	Aqueous Humor	Lens	Vitreous Humor	Retina
230	2.7				
235	10.8				
240	19.0				
245	26				
250	26				
260	26				
265	26.5				
270	28.7				
275	30.7				
280	33.2				
285	41.5				
290	51.5	2	0.4		
295	63.0	8.7	3.2		
300	70	27	14.3		
305	75	50	37		
310	78	64	50.5		
320	81	78	74	33	0.29
330	84	80	76.6	52	0.45
350	86.5	86	82.5	1.82	1.62
360	88.5	88	84.5	4.2	3.8
370	89.5	90	87	12.1	11.0
380	93*	91.2	88.2	28.2	25.8
390	94*	92.8	91.4	48.5	44.6
400	94.5	94	93	68.5	63.5
450		96	96	84	80.5
500		96	96	86.5	84.0

\*By extrapolation

radiations. Such an interpretation is consistent with the highly cellular nature of the corneal epithelium. The relatively thick absorptive layers of the other ocular components obscure any absorption peaks, so that the nature of the absorbing constituents cannot be inferred from the curves.<sup>6</sup> Presumably, the radiations are absorbed primarily by mucoid and collagen in the cornea, by albumin and globulin in the aqueous and vitreous humors and by the alpha and beta crystalbumin and albuminoid in the lens.

On the assumption that the sensitivity of the lens epithelium to injury at any wavelength is the same as that of the corneal epithelium, the minimal amount of radiant energy to which the eye would have to be exposed

<sup>6</sup> Cogan, D. G., and Kinsey, V. E. Action Spectrum of Keratitis Produced by Ultraviolet Radiation, *Arch. Ophth.* **35**: 670 (June) 1946. Moon, P. *Scientific Basis of Illuminating Engineering*, New York, McGraw-Hill Book Company, Inc., 1936, p. 30.

before minimal damage would occur to the lens can be estimated from the data in figure 2, provided the spectral distribution of the radiant energy is known. The method of making such an estimation is as follows. The effectivity of radiations at wavelengths  $\lambda$  for producing injury to the cornea may be represented by the equation  $\text{Eff}\lambda_c = E\lambda S\lambda$  where  $E\lambda$  is the energy incident on the outside of the eye and  $S\lambda$  the sensitivity of the structure. The total effectivity for a broad band of wavelengths is equal to the sum of the effectivities for each wavelength. The effectivity for producing injury to the lens is given by  $\text{Eff}\lambda_l = E\lambda I\lambda S\lambda$ , where  $I\lambda$  is the percentage of the total energy incident on the anterior surface of the lens. In like manner, the total effectivity for a broad band of wavelengths for the lens is the sum of the effectivities for each wavelength. The dose to which the eye would have to be exposed to produce minimal damage to the lens is the amount necessary to injure the cornea multiplied by the ratio of the total effectivities.

The procedure may be illustrated in the case of an eye exposed to sunlight. The distribution of the radiant energy in the ultraviolet end of the spectrum is shown in column 2 of table 2. The other values in the

TABLE 2 — *Relative Effectivity of Radiant Energy on the Cornea As Compared with the Lens Epithelium*

$\lambda$	$E\lambda$	$I\lambda$	$S\lambda$	$E\lambda I\lambda S\lambda$	$E\lambda S\lambda$
Wavelength Millimicrons	Energy Units	Percentage	Percentage		
290	0	0	97	0	0
292.5	1	1	81	0.81	.81
295	3.3	3.2	57	6.0	188
297.5	7.5	6.5	44	21.4	330
300	14.8	14.5	32	68.6	472
302.5	45	30	23	310	1,030
305	98.7	44	11	477	1,086
307.5	325	50	3	487	975
310	550	57	0	0	0
Total effectivity*				1,369	4,162
Ratio				$\frac{4,162}{1,369} = 3.02$	

\*Total effectivity expressed in arbitrary units

table are estimated from figure 2. The total effectivity for the cornea expressed in arbitrary units will be seen to be 4,162, while that for the lens is 1,369 and the ratio of the two is 3.02. It may be concluded, therefore, that the eye would have to be exposed to three times the dose necessary to produce minimal damage to the cornea before minimal injury to the lens could be encountered.

Still higher ratios would be encountered with other sources of ultraviolet radiation in which parallelism between the amount of energy coming from the source and the proportion of energy incident on the lens is not as great as it is in the case of the sun. It is evident, for example, that if a source of ultraviolet light emitted radiations shorter than 290 millimicrons

the ratio between the amount of energy needed to produce damage to the cornea and that required for the lens would tend to become infinite, since essentially no ultraviolet radiation would reach the lens

Incidentally, the studies of Verhoeff and Bell,<sup>7</sup> in which they exposed eyes to ultraviolet radiation from an arc lamp, experimentally confirmed the conclusions arrived at here, namely, that damage to the lens could result only after severe injury had been produced to the cornea

It is evident from the absorption curves that so little ultraviolet radiation in the abiotic range reaches the retina that damage from these rays would be extremely unlikely unless the sensitivity of the retina to ultraviolet radiation is much greater than that of other tissues. Experimental evidence in support of this conclusion also comes from the investigations of Verhoeff and Bell, who were unable to detect injury to the retina in monkeys and man after exposure to various doses of ultraviolet radiation

#### SUMMARY AND CONCLUSIONS

The ultraviolet absorption spectrums of various components of the rabbit eye have been measured. The limit of transmission for the whole eye is approximately 330 millimicrons, that for the lens, 310 millimicrons, and that for the aqueous and vitreous humors and cornea, separately, approximately 280 millimicrons.

Measurements of the absorption of ultraviolet radiations by the corneal epithelium indicate that the chief absorbing element is nucleoprotein, its limit of transmission being less than 230 millimicrons.

The minimal amount of radiant energy from the sun to which the eye would have to be exposed before minimal damage would occur to the lens was calculated to be about three times the dose necessary to produce minimal damage to the cornea.

The results suggest that so little ultraviolet radiation in the abiotic region reaches the retina that damage from these rays would be extremely unlikely.

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<sup>7</sup> Verhoeff, F. H., and Bell, L. The Pathological Effects of Radiant Energy on the Eye, *Proc. Am. Acad. Arts & Sc.* **51**:629, 1916.

Miss Jane Whitney gave technical assistance.

## REAL SIGNIFICANCE OF CENTERING A CONTACT LENS

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The prevailing method among physicians when centering a contact lens has been to center the cornea of the lens with the cornea of the eye. The cosmetic appearance of the lens is best when the cornea of the lens is thus centered with, and in a way superimposed on, the cornea of the eye. But the optical effect of such centering may or may not be the best. Pronounced displacement of the lens cornea with reference to the cornea of the eye will practically always impair vision. But a slight displacement may definitely improve vision, sometimes considerably so, after the lens has been worn for some time.

To understand what happens, one must consider the optical system of the eye alone and that when a contact lens is worn. The two components of the optical system of the eye are the cornea and the crystalline lens. The latter, as has been shown by Gullstrand, may best be considered as consisting of three lenses, i e, two concave meniscus lenses enclosing a double convex nuclear lens.

Now, one of the most important requirements for perfect imagery in an optical system is that the component elements be properly centered on a common axis. In the eye such centering is always more or less approximate. What has been termed the optic axis is the imaginary line on which the optical elements are more or less centered. The extent of this centering certainly varies in different eyes and would explain, in part, differences in visual acuity. A spectacle lens adds another element to the optical system of the eye, but it does not materially change the intrinsic centering, good or bad, of the optical system.

When a contact lens is placed on the eye, the cornea of the lens replaces the cornea of the eye in a very real sense. Like the cornea of the eye, it is a thin meniscus lens of high power, separating air from a solution which is practically like the aqueous. The cornea of the eye, situated between the buffer solution and the aqueous, not only loses all its positive refractive power but generally acquires a low minus effect. Its power in situ is approximately  $-0.50$  to  $-0.75$  D. The optical system of the eye is now made up of the lens, cornea and the crystalline lens. The cornea of the eye is merely a low power minus lens placed inside the system between

its two components. The effect of this low power ocular cornea (of less than 1.00 D) is practically negligible with reference to the centering of the optical system, which has a total power of between 50 and 60 D.

It may be *apropos* to emphasize here that the power of a contact lens in air has little relation to its power when placed on the eye. In the latter position it is always a very strong convex meniscus lens, comparable to the power of the cornea. Even though it is a plano or a minus lens in the air, it becomes a powerful convex lens when placed on the eye, roughly between +35.00 and +45.00 D.

To get the best optical effect of the contact lens, the lens cornea should be centered with the crystalline lens, which is the other major component of the optical system. Objectively this is impossible, but subjectively it can be done. Objectively, one can center the cornea of the lens with the cornea of the eye. But the centering of the lens cornea with the crystalline lens will depend on how well centered the cornea of the eye is with reference to the crystalline lens. Subjectively, a better centering of the whole optical system may sometimes be obtained by watching the direction of the so-called lag.

Every contact lens lags a little behind the movement of the eye. This may be due to action of the lid or to inertia or to both. A patient wearing a contact lens which seems properly centered in the primary position with reference to the cornea of the eye may see better when he turns his head, say, to the right. What has happened? As his head turned to the right, the eye, say it is the right eye, has turned to the left, that is, nasally. The lens, lagging slightly behind the movement of the eye, is now displaced slightly toward the temple. If this produces better vision, the lens in this position must be more accurately centered with the crystalline lens in the eye than it was before. This maneuver would constitute the subjective centering of a contact lens, which is centering it with reference to the crystalline lens, as against objective centering, which is centering it with reference to the cornea of the eye.

It may be added that the visual axis, the line along which vision actually takes place, is generally oblique to the optic axis by the so-called angle alpha.

This obliquity increases the general aberrational defects of the retinal image and must cause some lowering of visual acuity. But the visual axis is a secondary axis of the optical system of the eye, and it may be postulated that when the optical components are more perfectly centered on the principal, or optic, axis, the image along a secondary axis will be better focused. Of course, it is possible that, taking into consideration the complex structure of the crystalline lens, as well as other aberrational factors, a less perfect centering on the optic (principal) axis may give a better retinal image along the visual (secondary) axis. In either case,



however, the effect is ascertainable only by a subjective centering of the contact lens

The fact that a contact lens may introduce a new centering and a new optic axis will explain some commonly observed facts. Many patients see somewhat "differently" with a contact lens, there is a different "feel" to the seeing process. Vision frequently improves after a contact lens has been worn for some time over what it was when the lens was first put on. One must visualize in these cases a sort of transformation of one type of eye, with all its aberrational effects, which the patient has learned to interpret, into another type of eye, with different aberrational effects.

One sometimes sees cases of mild conical cornea in which vision is greatly improved by a contact lens. The ophthalmometer will show a highly curved corneal surface but little, if any, irregularity. The striking improvement in vision produced by a contact lens in these cases is probably due to a better centering of the cornea of the lens with the crystalline lens than was obtained with the cornea of the eye. Many other phenomena in work with contact lenses will become clearer if the physician realizes that the contact lens reduces the cornea of the eye to an insignificant position, and itself becomes the most important element in the new optical system of the eye. This is entirely different from the accessory effect on the optical system of the eye produced by a spectacle lens.

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## SYNDROME OF UNILATERAL RECURRENT ATTACKS OF GLAUCOMA WITH CYCLITIC SYMPTOMS

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In order to form a complete picture of a case of glaucoma, it is essential to observe the patient at frequent intervals and over a relatively long period. A case, ideal in this sense, presented itself in a physician who lived in the immediate vicinity and thus was able to visit our office at the earliest indication of an oncoming attack. This patient had recurrent unilateral attacks of ocular hypertension associated with cells in the aqueous and a few keratic precipitates, which disappeared shortly after the tension returned to normal. The time relation of the appearance of the hypertension and the cyclitic phenomena could be accurately studied. Also, an attempt was made to evaluate the response of the symptoms to various drugs.

This case aroused our interest in the relation between glaucoma and cyclitis. A survey of our glaucoma files disclosed 7 more such cases, and a new case occurred in our practice during the preparation of this paper. All these 9 cases, which were followed for periods varying from one month to nineteen years, were characterized by a striking uniformity in symptoms, course of the disease and response to treatment.

The chief features of this syndrome may be briefly described as follows:

- 1 The disease is unilateral. In 3 cases there was some degree of heterochromia, and in each instance the lighter-colored eye was involved. In 3 cases anisocoria was present, the affected eye having the wider pupil.

- 2 The presenting symptom is usually slight discomfort, colored halos or blurring of vision. However, no symptoms may be present. There is no pain. Vision is usually good, even at the height of the attack.

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Read at a meeting of the New York Society for Clinical Ophthalmology, May 5, 1947.

3 The eye is white, or a few dilated conjunctival vessels may be visible. Ciliary injection is never present. If the tension is very high, mild congestion of the sclera or edema of the corneal epithelium may be noted.

4 Ocular hypertension may appear a day or so before, or simultaneously with, cells in the aqueous. It is followed within the next twenty-four hours by from one to twenty small, well defined, unpigmented precipitates on the posterior surface of the cornea. These soon begin to disappear, and, if the hypertension persists, fresh ones may appear. After subsidence of the hypertension, the precipitates fade away within a few days to a month. Although precipitates are present as a rule, they may be absent during some of the attacks (case 3). At no time is there more than a trace of aqueous flare. Posterior synechias are never formed.

5 The angles were open in all 4 cases in which gonioscopic studies were made. In 2 cases they were wide and in 2 moderately narrow.

6 The individual attacks of ocular hypertension have lasted from a few hours to one month, but rarely over two weeks. Attacks which have been observed without treatment have cleared within two weeks. It is possible that overtreatment, whether with miotics or with mydriatics, may prolong the attack.

7 Episodes may occur with varying frequency and without any apparent cause. One patient has had five attacks in a period of eight months, another has been having two or three attacks a year for the past thirteen years, and still another had four attacks up to thirteen years ago and has been free from symptoms since. The visual fields may show enlargement of the angioscotomas during the acute phase. In 1 case, in which there were deep cupping and pallor of the nerve head, the field became progressively contracted. In all other cases the field remained normal during the course of the disease. During the intervals of freedom from glaucoma, provocative tests, such as the liability and the water-drinking test, give negative results, and there are no signs or symptoms either of iridocyclitis or of glaucoma.

8 Treatment does not seem to shorten the course of the attack. One-half to 2 per cent pilocarpine hydrochloride N. F. may lower the tension temporarily. Physostigmine and stronger concentrations of pilocarpine usually give rise to extreme discomfort and pain and may even cause a rise in tension. Homatropine and atropine usually have no pronounced effect on the tension, but, apparently, they are not detrimental to the eye. Epinephrine bitartrate, 2 per cent, and phenylephrine ("neo-synephrine") hydrochloride, 10 per cent, may produce an evanescent reduction of the tension. Since the attack is self limited, it

is safe to procrastinate and use no treatment (or placebo therapy) until the diagnosis has been established and the course has been followed through at least one attack. Surgical intervention did not have to be resorted to in any of our cases. Kraupa<sup>1</sup> found that in 2 of his 4 cases surgical treatment did not affect the subsequent course of the disease, since the patients continued to have acute attacks.

#### REPORT OF CASES

CASE 1—E W, a white physician aged 43, consulted an ophthalmologist because, for the first time, he had experienced blurring of vision for three hours. The tension in the right eye was 70 mm (McLean), while that in the left eye was normal. A diagnosis of primary glaucoma was made. With use of pilocarpine, the tension dropped to normal but soon rose to 50 mm (McLean). After several days of therapy with miotics, keratic precipitates were observed in the right eye, and the diagnosis was changed to that of secondary glaucoma. Use of pilocarpine was stopped after one week of treatment. Three days after the discontinuation of the miotic (or ten days after the onset), the tension was 25 mm (McLean). The patient was free from symptoms except that the left pupil was dilated and accommodation was temporarily suspended, owing to the inadvertent use of atropine sulfate. During this attack his temperature, which was normally below 98 F, rose to 99 F on three occasions. The white blood cell count rose from 7,000 to 11,100 per cubic millimeter.

When the patient was first seen by us, on Aug 19, 1946, two weeks after the onset, the tension was 18 mm (Schiotz) in the right eye and 22 mm in the left eye. The right pupil was 3.5 mm and the left 5 mm in diameter (atropine mydriasis). Both irises were brown, but the right was of slightly lighter color than the left. In the right eye, a few nonpigmented, small, well defined keratic precipitates were present on the posterior surface of the cornea. There were no cells in the aqueous and no posterior synechias. The media were clear, and the fundus was normal. The left eye was normal. Vision was 20/15 in each eye with a —1.75 D sphere for the right eye and a —2.25 D sphere for the left eye. Gonioscopic examination of both eyes showed wide angles throughout. The lower part of Schlemm's canal contained blood.

The patch test gave a 3 plus reaction to tuberculin. A roentgenogram of the chest showed no evidence of tuberculosis. Brucellosis was excluded by serologic study. The Wassermann reaction of the blood was negative.

The patient gave a history of old nongonococcal prostatitis and of mild and variable hypertensive vascular disease, as well as of hay fever, of fifteen years' duration, associated with asthma during the first two years.

He remained free from symptoms until October 7, when he presented himself two hours after he had begun to see rainbows with his right eye. At this time tension was 49 mm in the right eye and 20 mm in the left eye. The eye was white. There were a few deposits on the posterior surface of the cornea and numerous cells in the aqueous, but no flare was noted. With 1 drop of 10 per cent phenylephrine hydrochloride N N R, the right pupil was almost maximal. The tension fell to 41 mm in forty-five minutes and then dropped to 22 mm within four hours. The following morning, tension in the right eye was 24 mm, the cells were less numerous but the deposits had increased in number.

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<sup>1</sup> Kraupa, E. Ocular Hypertension in Acute Angioneurosis of the Ciliary Body ("Glaucoma Allergicum"). Its Relationship to Cyclitic and Heterochromic Glaucoma, *Arch f Augenh* 109:416, 1935.

Another ophthalmologist saw the patient that evening and, finding the tension normal, instilled a drop of homatropine hydrobromide into the right eye That night the patient had an uncomfortable sensation in his right eye The following morning, October 9, the right pupil measured 5 mm and the tension was 53 mm (Schiotz), while the left pupil was normal The eye was white except for a few dilated conjunctival vessels Cells were seen in the aqueous, and a few fresh deposits were visible on the posterior surface of the cornea This time 10 per cent phenylephrine hydrochloride failed to lower the tension, but 2 per cent pilocarpine hydrochloride brought it down to 20 mm within two hours A 3 D increase in myopia was noted, which lasted two hours Pilocarpine hydrochloride, 2 per cent, given every four hours, controlled the tension No cells were observed after October 10 (three days after onset of the second attack) The keratic precipitates, however, persisted until October 24 Miotics were discontinued on October 16, and the tension remained even lower than that in the left eye

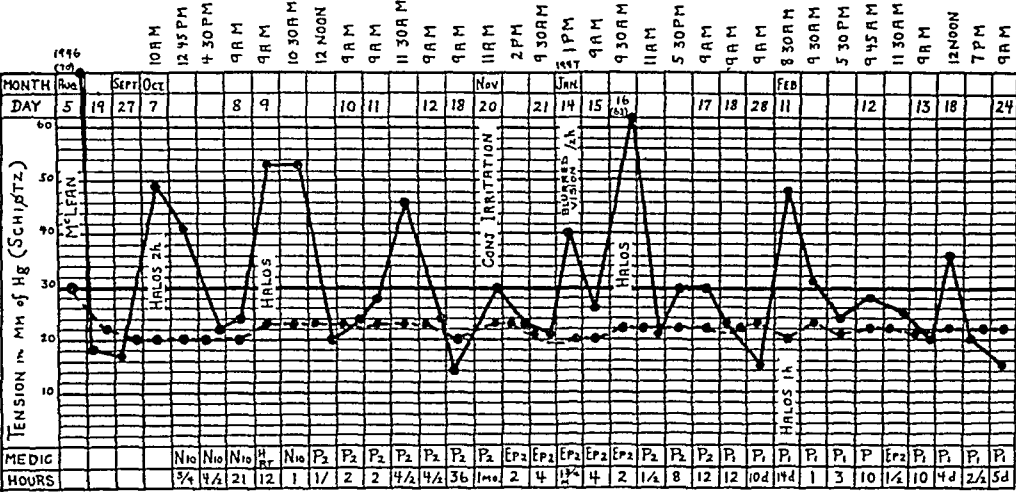


Chart 1 (case 1) —Tension curve for a patient with glaucomatocyclitic crises in the right eye  $N_{10}$  indicates phenylephrine hydrochloride, 10 per cent,  $H_1$  homatropine hydrobromide, 1 per cent,  $P_2$ , pilocarpine hydrochloride, 2 per cent,  $Ep_2$  epinephrine bitartrate, 2 per cent,  $P_1$ , pilocarpine hydrochloride, 1 per cent

In this chart, and in charts 2 to 5, the curve for the right eye is shown by the solid line, that for the left eye, by the broken line

The third episode occurred on Nov 20, 1946, when the patient experienced slight conjunctival irritation in his right eye The right pupil was 1 mm larger than the left Tension was 30 mm in the right eye and 23 mm in the left eye There were deposits on the posterior surface of the cornea and numerous cells in the aqueous The patient suggested the use of 2 per cent epinephrine bitartrate Within three hours the tension dropped to 23 mm He had no visual disturbance, and the irritat on promptly disappeared The tension remained normal On Jan 8, 1947 only two minute keratic precipitates remained

On Jan 14, 1947, one-half hour after the onset of blurring of vision and irritation in the right eye, the tension measured 40 mm in the right eye and 20 mm in the left eye There were no cells in the aqueous, and the eye was white The two precipitates which had been noted previously were still present Epinephrine bitartrate, 2 per cent, was used every four hours, and the following morning the tension was 26 mm in the

right eye and 20 mm in the left eye, but this time a few cells were present in the aqueous and about a dozen new keratic precipitates were noted. In spite of the continued use of epinephrine bitartrate, the tension rose to 62 mm on the following day (third day after onset of attack). Pilocarpine hydrochloride, 2 per cent, brought the tension down to 21 mm within an hour and a half and increased the myopia by 4 D. The tension fluctuated around 30 mm until January 18 (unaffected by use of pilocarpine, epinephrine or phenylephrine). It then dropped sharply to between 15 and 18 mm. On February 4, only one keratic precipitate was visible.

The fifth attack occurred on February 11. It had a similar course. Again, cells were seen and fresh precipitates noted. They disappeared within ten days.

Pupillographic studies, made on two occasions by Dr. Otto Lowenstein, showed a curve which indicated sympathetic phenomena, such as are noted in cases of hypertensive vascular disease. A diurnal tension curve was normal. The water-drinking test, used as a provocative, gave negative results. The tension curve is shown in figure 1.

CASE 2—M. S., a dentist aged 41, had the first attack of hazy vision and colored halos in the left eye in September 1934, when he was 28 years of age. An ophthalmologist made a diagnosis of low grade cyclitis with secondary glaucoma and treated him with atropine and salicylates. The attack subsided within a few days.

A similar episode occurred in September 1938. A different ophthalmologist treated him at first with pilocarpine for three weeks, then, when keratic precipitates were noted, atropine was substituted. This attack subsided after six weeks. Third and fourth attacks, each lasting three weeks, occurred in August 1939 and February 1940, respectively. In these attacks treatment was with homatropine.

The patient was first seen in this office on May 11, 1940, on the third day following the onset of hazy vision and colored halos in the left eye. The day prior to his visit, he had used 1 per cent pilocarpine hydrochloride and the symptoms subsided after one hour. Examination showed vision to be 20/20 in the right eye with a correction of  $-0.75$  cyl, axis 170, and 20/15 in the left eye with a correction of  $+0.50$  sph  $-1.00$  cyl, axis 180. Both eyes were white. The irises were brown and of the same color. The pupils were regular and reacted to light. The right pupil measured 3.5 mm and the left 4 mm. The fundi were normal. Examination with the slit lamp revealed twelve minute keratic precipitates in the left eye. Both anterior chambers were of normal depth. Tension was 15 mm in the right eye and 31 mm in the left eye. The fields and blindspots were normal.

A patch test gave a negative reaction to tuberculin. Medical examination revealed nongonococcic urethritis. The electrocardiogram and the basal metabolic rate were normal. Roentgenograms of the sinuses, teeth and chest revealed a normal condition. The patient gave a history of hay fever due to ragweed.

He was given a 1 per cent solution of pilocarpine hydrochloride to use three times a day in his left eye. On May 15, 1940 the tension in this eye was 22 mm. The precipitates were gone by June 10 (one month after the onset).

The patient returned a few times for examination. The tension was always normal, and no signs of cyclitis were present. On October 15, he was seen three hours after he began to see rainbows and twelve hours after onset of hazy vision in the left eye. The eye was white, but the tension was 38 mm. Tension in the right eye was 17 mm. Vision was normal in both eyes. Examination with the slit lamp revealed eight fresh, discrete, small keratic precipitates. Two hours after use of 10 per cent pilocarpine hydrochloride, tension in the left eye was 31 mm. He used 2 per cent pilocarpine hydrochloride every two hours, and the following day the tension was normal. By November 10 all signs of



The family history revealed that one other member of the family, an aunt on the paternal side, had glaucoma. The patient had been subject to severe right-sided migraine headaches for the past two years. He has a highstrung, neurotic nature.

On April 14, 1939, he awoke with foggy vision in the left eye, followed by his seeing colored halos. The tension was 22 mm in the right eye and 70 mm in the left eye (three days previously the tension had been 22 mm in each eye). The eye was white. Vision was 20/30 in the left eye. There were cells in the aqueous and a few white precipitates on the posterior surface of the cornea. He used pilocarpine and physostigmine at frequent intervals. Tension fluctuated between 30 and 60 mm but was normalized by May 5, 1939. The deposits had disappeared by May 24, 1939.

The next episode occurred on Feb. 11, 1940, when the patient began to see rainbows with his left eye. After a few instillations of 1 per cent pilocarpine hydrochloride, the halos disappeared. The next day tension in the left eye was 45 mm. Examination with the slit lamp at this time did not reveal any cells in the aqueous or keratic precipitates. When the hypertension failed to recede after two days, he began to use 20 per cent methacholine chloride with 5 per cent neostigmine methylsulfate. The tension returned to normal on February 25. No precipitates or cells appeared during the entire course of this attack.

On Dec. 20, 1940, the tension rose to 42 mm and was quickly controlled with pilocarpine. No cells or deposits were noted with this attack. The tension curve is shown in chart 2.

The patient has been free from symptoms and tension has remained normal up to the time of writing. Pupillographic studies showed a bilateral curve similar to that associated with primary glaucoma. He was carefully studied for foci of infection. One abscessed tooth was extracted in May 1939, and he received a course of injections of autogenous vaccine. This treatment failed to influence the course of the attacks. He never saw halos when the tension was below 40 mm, although occasionally he had no visual disturbance with a tension as high as 60 or 70 mm. Miotics increased his myopia by as much as 4 D.

CASE 4—M. C., a white man aged 45, was first seen on April 21, 1944. He gave a history of having had attacks of blurred vision and seeing colored halos in the right eye every four to six months for the past ten years. These attacks would last three to ten days and wear off without any treatment, leaving no sequelae.

The present attack began on April 18, and had been preceded by a similar episode ten days previously. The patient decided to consult a physician because, for the first time, he had experienced two attacks within so short a period. He had never had any symptoms in the left eye. Examination showed 20/20 vision in the right eye with a correction of +3.50 sph +0.25 cyl, axis 90, and 20/200 in the left eye with a correction of +3.75 sph +1.75 cyl, axis 115. The left eye had been amblyopic since childhood. The right pupil was larger than the left and reacted sluggishly to light and in accommodation. Tension was 65 mm (Schiotz) in the right eye and 28 mm in the left eye. The fundi were normal. The anterior chambers were of normal depth. Examination with the slit lamp showed a few deposits on the posterior surface of the right cornea. The left cornea was normal. He was given 2 per cent pilocarpine hydrochloride, to be used four times a day. The drops caused pain and blurring of vision, which lasted two hours. The tension continued to be elevated all this time, despite the drops. On May 1 the deposits were much fewer. He was not seen until June 15, when no precipitates were found.

The patient returned again on April 26, 1946, two days after he began to have blurred vision and see rainbows in his right eye. He used pilocarpine of his own accord, but the eye felt worse and he became alarmed. He had had three attacks since he was



last seen (June 15, 1944) The first one, in September 1944, lasted three days and subsided with the use of pilocarpine The other two, which occurred on Jan 1 and Nov 7, 1945, lasted one week each

There was slight scleral congestion The cornea was somewhat steamy The right pupil was larger than the left but reacted normally The fundus was clearly visible and was normal The slit lamp showed three deposits on the posterior surface of the right cornea The tension was 70 mm in the right eye and 28 mm in the left eye Phenylephrine hydrochloride, 10 per cent, and pilocarpine hydrochloride, 5 per cent, failed to affect the tension In view of this fact, and because of the self-limited nature of the crises, the patient was instructed to use nothing but acetylsalicylic acid and ice applications On May 3 the symptoms subsided, and the tension remained normal until Dec 25, 1946 At this time he consulted another ophthalmologist, who found that the tension was 50 mm in the right eye and that precipitates were present on the posterior surface of the cornea This attack subsided in ten days

The patient was last seen on March 9, 1947, when the right eye appeared perfectly normal The fields and blindspots were normal Gonioscopic examination showed the angles to be moderately narrow The right pupil was 0.5 mm larger than the left No heterochromia was noted Pupillographic studies showed central sympathetic phenomena The patient has no systemic disease and is not subject to any allergic manifestations

CASE 5—E T, a white woman aged 32, came to our office on Oct 30, 1939 She gave a history of an attack of blurred vision in the right eye on Aug 15, 1939 Another ophthalmologist had prescribed pilocarpine, and the attack wore off in one day She continued to use pilocarpine and physostigmine, but she had another attack in the right eye on October 23 The tension did not respond to miotics at this time, and surgical intervention was advised but was not carried out because the eye began to improve soon thereafter

The patient was slender and somewhat underweight and appeared tense and excitable She had no family history of glaucoma No history of allergy was given Examination showed vision of 20/20 in each eye with a -0.75 D sphere The pupils were pinpoint, owing to the use of miotics Tension was 31 mm in the right eye and 20 mm in the left eye Examination with the slit lamp showed that the anterior chambers were of normal depth There were about six small, discrete, white deposits on the posterior surface of the right cornea The fields and blindspots were normal Thorough medical examination disclosed no pathologic condition Roentgenograms of the sinuses revealed nothing abnormal, but two impacted teeth were discovered and removed Use of pilocarpine hydrochloride, 1 per cent, twice a day, was continued The symptoms did not recur, and the tension remained normal The keratic precipitates disappeared by November 24 (four weeks after onset)

The patient remained well until Jan 1, 1940, when she noticed haziness of vision and rainbows in the right eye This attack coincided with the end of the menstrual period She was seen on January 3, when the tension was 42 mm in the right eye and 22 mm in the left eye Vision was normal, and the eye was white There were eight minute deposits on the posterior surface of the right cornea Tension subsided by January 5 with the use of pilocarpine, and the deposits disappeared by January 23 She has remained well since this time

CASE 6—E D, a white man aged 59, a pharmacist, had been subject to recurrent attacks of slight pain and blurring of vision every few months for ten to fifteen years prior to his first visit to our office, on March 9, 1936 The present attack occurred on March 2 and was the severest he had yet had When he was first seen by another

ophthalmologist, on the fourth day of his attack, a diagnosis of acute glaucoma was made and operation was advised. A second ophthalmologist, however, treated him with 2 per cent pilocarpine hydrochloride and 0.25 per cent physostigmine salicylate. The attack subsided and vision improved. Thus, the attack lasted one week. The patient had a mild hypertensive vascular disease. There was no family history of glaucoma.

Examination showed vision of 20/20 in the right eye with a correction of +0.25 sph +0.50 cyl, axis 180 and 20/15 in the left eye with a correction of +1.00 D sph +1.00 cyl, axis 75. The right eye was normal in appearance except that the right iris was gray and the left one brown. The right pupil was smaller than the left because of the use of pilocarpine. The right disk was pale and showed moderate glaucomatous excavation. The left eye was normal. Examination with the slit lamp showed two unpigmented deposits on the posterior surface of the right cornea. The tension was 22 mm in each eye. There was absence of the upper half of the right field, with a pronounced contraction of the lower half. The left field was normal.

During the two years following this attack, the patient used pilocarpine irregularly once or twice a week, the tension remained normal, and no keratic precipitates were seen. On June 7, 1938, the tension was found to be 36 mm. The patient had had symptoms of blurred vision for the past few days and, although the eye (right) was white, examination with the slit lamp showed several fresh, well circumscribed deposits on the posterior surface of the cornea. Tension responded to 1 per cent pilocarpine hydrochloride, and the symptoms subsided.

On June 14, 1940 another routine check-up revealed that tension in the right eye was increased. In July the tension was back to normal, but it rose again on Oct. 25, 1940, and fresh deposits were noted. The hypertensive phases became more frequent after November 1940. Although the patient did not have any symptoms, the visual field in his right eye rapidly diminished, and vision was reduced to light perception by June 1941. He instilled pilocarpine irregularly, and only when he thought he had increased tension. This drug, although it usually lowered the tension, did not prevent attacks.

CASE 7—R. M., a white housewife aged 51, began to have attacks of edematous swellings in various parts of the right side of the face and neck, associated with headache and misty vision of the right eye, in the summer of 1927 (She was 31 years of age at this time). An ophthalmologist found the tension in the right eye to be 70 mm and prescribed pilocarpine. The following day the tension was normal. She continued to use low concentrations of pilocarpine. Her tension remained normal, but in June 1933 she complained of blurred vision in the right eye, of two days' duration. The eye was white. The tension was 43 mm, and a few fresh keratic precipitates were present in the right eye. This time she was given homatropine, and the tension subsided within three days. Medical examination showed no foci of infection. The precipitates disappeared within three weeks. In February 1934 she had a similar episode. Tension was 31 mm, and a few fresh deposits were noted. This attack improved in a few days with the use of homatropine. The drug was continued prophylactically for nine months. During the next year she had another attack and was treated with pilocarpine.

When she came to this office, on May 23, 1942, she had been using miotics in the right eye for the past few years. Tension was 17 mm in the right eye and 19 mm in the left eye. Vision was 20/25 in each eye with a correction of -2.50 cyl, axis 45 for the right eye and -1.75 sph -2.00 cyl, axis 135 for the left eye. The irises were brown and of the same color. The fundi were normal. The media were clear. The anterior chambers were of normal depth, and gonioscopic examination showed that both angles were open and wide. Examination with the slit lamp revealed nothing abnormal.

The patient has been followed at monthly intervals up to the present. At no time during this period, from 1942 to 1947, were any deposits noted on the cornea or were cells present in the aqueous, and the tension remained consistently normal in each eye. The patient has used 0.5 per cent pilocarpine hydrochloride twice a day in the right eye, mainly for psychologic reasons. During this time, her health has been good, but a mild hypertensive vascular disease developed.

Pupillographic examination on March 13, 1947, after the patient had discontinued use of pilocarpine for one week, showed a bilateral curve similar to that found in cases of primary glaucoma. The lability test produced no increase in tension. The fields were normal.

CASE 8—L. E., a housewife aged 43, first seen on March 12, 1947, one week after the onset of blurred vision and "itching" in her right eye, had had a similar attack one year before but did not consult a physician. This time she visited an ophthalmologist, who found a tension of over 70 mm. in her right eye. The eye was white, and no keratic precipitates were noted at this time. He instilled a drop of 0.5 per cent physostigmine salicylate into her right eye, whereupon the eye became inflamed and tender to touch. The tension remained high. Examination by us the following day revealed that her right eye was white and that tension was 77 mm. in the right eye and 24 mm. in the left eye. The iris of the right eye was a light gray, whereas that of the left eye was brown. Examination with the slit lamp revealed approximately seven translucent, small, round precipitates on the posterior surface of the cornea of the right eye. The left eye was normal. The fundi and fields were normal. Vision was 20/20 in each eye without correction. Gonioscopic examination showed that both angles were moderately narrow, the corneoscleral trabeculum was somewhat pigmented and Schwalbe's line was indistinct. Phenylephrine hydrochloride, 10 per cent, lowered the tension in the right eye to 56 mm. She was instructed to do nothing to the eye except to apply cold compresses. She was comfortable thereafter, and the tension gradually fell, becoming normal by March 19 (fifteen days after onset). On March 26 the keratic precipitates were disappearing. The pupils were equal in size.

Her medical history was interesting. For many years she had been subject to attacks of migraine and crying spells. Her blood pressure was 160 systolic and 100 diastolic. In 1937 she had a cholecystectomy for typical recurring attacks of cholecystitis. The attacks continued to recur for several years after the operation. Each episode was followed by urticaria on the right side of the face and neck, extending to the right half of the forehead and the back of the right hand. The urticaria was associated with tearing of the right eye. No cause was found for these urticarial attacks. The patient did not have hay fever. Pupillographic examination showed central sympathetic phenomena similar to those found in patients with hypertensive vascular disease.

CASE 9—B. T., a woman aged 60, a bookkeeper, had been subject to recurring attacks of blurring of vision in the left eye since 1937. These attacks lasted a few days to one week and recurred every eight to twelve months. Several years ago, she was given 2 per cent pilocarpine hydrochloride by an ophthalmologist, but she did not use this drug regularly because it engendered blurring of vision. Her sister has been under our care for chronic simple glaucoma for a number of years.

The patient came to this office on March 10, 1945, two weeks after the intermittent appearance of rainbows and blurring of vision, which began about one hour after arising in the morning and disappeared toward evening.

Examination revealed vision of 20/20 in each eye with a correction of -0.25 D sphere for the right eye and -0.25 sph -0.25 cyl, axis 150 for the left eye. The ten-

sion was 25 mm in the right eye and 84 mm in the left eye. The ciliary body was not injected, but the sclera showed slight generalized congestion. Ophthalmoscopic examination showed a large, irregular-shaped opacity in the vitreous of the left eye in front of the disk. The nerve head was of normal color, but slightly cupped. The right fundus was normal. Examination with the slit lamp revealed four unpigmented deposits on the posterior surface of the left cornea and bedewing of the corneal epithelium. The patient was given 2 per cent pilocarpine hydrochloride, and the tension dropped to 33 mm within two hours. The tension returned to normal in two days, and the deposits disappeared within two weeks.

#### COMMENT

The importance of the recognition of this syndrome lies in its forming a link between the primary and the secondary glaucomas, since it cannot be classified in either category. For this reason, this group of cases assumes a significance far greater than is warranted by the low incidence of the syndrome.

A review of the literature reveals two papers dealing with this syndrome. Terrien and Veil<sup>2</sup> described a heterogeneous group of cases to illustrate the importance of careful examination with the slit lamp in every case of glaucoma. Among them were 3 cases, perhaps 4, which belonged to this type, and only 1 of these was followed sufficiently long to permit observation of more than one attack. The authors did not attempt to classify these cases except to place them in the general category of secondary glaucomas. Kraupa described 4 similar cases and recognized that they represented a distinct clinical entity (1935).<sup>1</sup> He noted the relation between heterochromia and this type of glaucoma. He reasoned that the underlying pathologic mechanism of both types (with and without heterochromia) is in some way related to the sympathetic nervous system and called it "glaucoma allergicum" for want of a better name. Since it is generally accepted that the autonomic nervous system plays a role in all glaucomas, we felt that this name would not circumscribe this special group of cases. Moreover, Kraupa's title carries etiologic implications which we are not yet prepared to corroborate or to disprove. There is no article in the English literature dealing with this syndrome. Kronfeld, in one of his papers,<sup>3</sup> mentioned a group of "cases of acute elevation of intraocular pressure occurring simultaneously with mild recurrent cyclitis." He mentioned them only to exclude them from a general discussion of secondary glaucomas because, in his opinion, this condition represents "a clinical entity." Since he did not define them further, it is difficult for us to know whether he

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<sup>2</sup> Terrien, F., and Veil, P. Certain So-Called Primary Glaucomas, *Bull. et mem. Soc. Franc. d'opht.* 42:349, 1929.

<sup>3</sup> Kronfeld, P. C. Gonioscopic Correlates of Responsiveness to Miotics, *Arch. Ophth.* 32:447 (Dec.) 1944.

referred to the syndrome discussed here. Textbooks on ophthalmology, including Duke-Elder's,<sup>4</sup> do not separate this type, and the more recent papers<sup>5</sup> dealing with the over-all relation of glaucoma to cyclitis take no cognizance of the specific symptomatology and clinical behavior of this entity.

According to the generally accepted teaching, the findings of keratic precipitates or cells in the aqueous stamps a case of glaucoma as secondary to uveitis. Some authors even regard the presence of pigment dust on the posterior surface of the cornea<sup>5</sup> or the anterior surface of the lens<sup>6</sup> as evidence of associated uveal involvement. Since a large proportion of normal persons, especially in the older age group, show such precipitates, this criterion has been discarded by more recent observers.

We wish to emphasize that the presence of keratic precipitates is only one of several factors which have a bearing on the pathogenesis and clinical course of a specific case of ocular hypertension. The classification of a case as one of secondary glaucoma does not of itself help one in the management or the prognosis. It has been stated by a number of writers that glaucomas secondary to uveitis are extremely variable and that their course is unpredictable. We feel, therefore, that if a homogeneous group of cases can be segregated from the general class of secondary glaucomas, it represents a definite advance in knowledge of this poorly understood subject.

This leaves the over-all relation of glaucoma to iridocyclitis still unsolved. A few clues, however, presented themselves in the course of this study.

Two patients, who have been followed for fourteen and nineteen years, respectively, showed a combination of true primary glaucoma and iridocyclitis.

CASE 10—A M, a housewife aged 67, was first seen in 1933 with acute iridocyclitis of the left eye, which was followed the next day by a similar inflammation of the right eye. She improved under treatment with atropine and scopolamine, but the ocular tension remained elevated. The eyes became quiet, and the patient did not return to the office until two years later. At this time she had tension of 65 mm. in each eye and deep cupping of both disks. The right field was normal, but the left field showed pronounced nasal contraction.

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4 Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 3288.

5 (a) Malling, B. *Relationship Between Iridocyclitis and Glaucoma*, *Acta ophth* 1:97, 1923. (b) Larson, H. *Relationship Between Iridocyclitis and Glaucoma*, *ibid* 1:345, 1923. (c) Fralick, F. B., Cooper, J. H., and Armstrong, R. C. *Uveitis with Secondary Glaucoma*, *Tr Am Acad Ophth* 47:92, 1942-1943. (d) Weekers, L. *Treatment of Ocular Hypertension Complicating Iridocyclitis*, *Arch d'opht* 53:166, 1936.

6 Risley, S. S. *Simple Glaucoma*, *Ann Ophth* 23:437, 1914.

The picture was that of chronic simple glaucoma without symptoms. An Elliot trephine operation on both eyes normalized the tension, and her status has remained unchanged to the present. The tension curve is shown in chart 3.

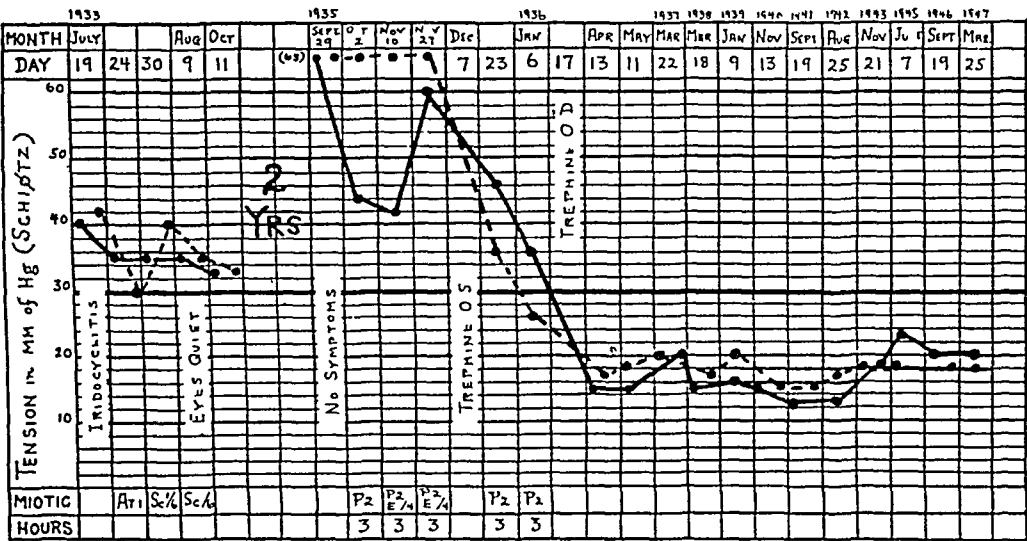


Chart 3 (case 10) —Tension curve for a patient with glaucoma simplex complicated by iridocyclitis in both eyes.  $At_1$  indicates atropine sulfate, 1 per cent,  $Sc$  1/6 scopolamine hydrobromide, 0.16+ per cent,  $p_2$ , pilocarpine hydrochloride 2 per cent,  $E\frac{1}{4}$ , physostigmine salicylate, 0.25 per cent.

CASE 11—M N, a business man aged 64, was first seen in 1929 with an acute attack of iridocyclitis and hypertension in his left eye. The eye was intensely injected. A 2 plus aqueous flare and keratic precipitates were present. He gave a history of having seen colored halos intermittently for two years.

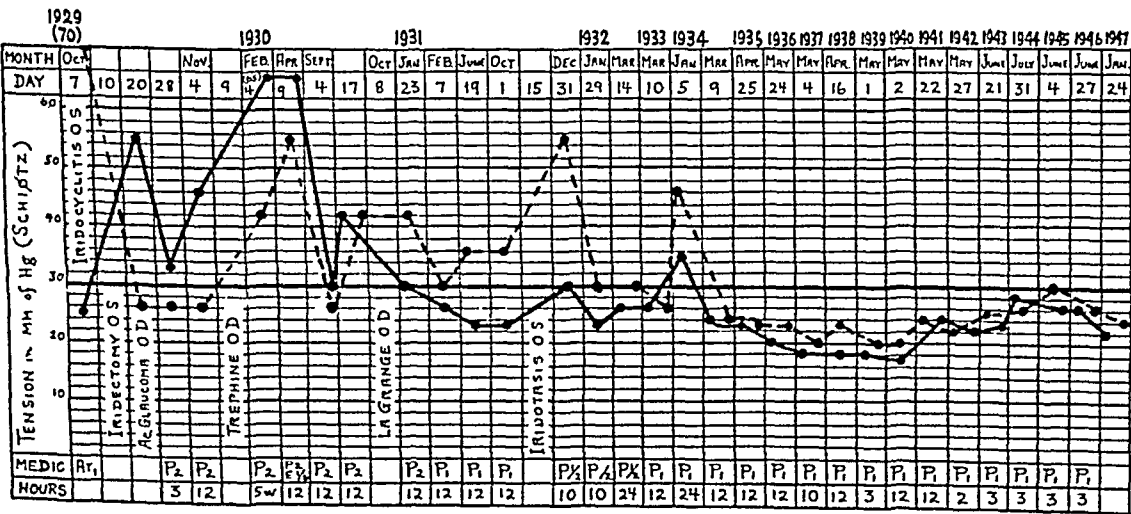


Chart 4 (case 11) —Tension curve for a patient with chronic congestive glaucoma complicated by iridocyclitis in the left eye.  $At_1$  indicates atropine sulfate, 1 per cent,  $P_2$ , pilocarpine hydrochloride, 2 per cent,  $L$  1/6, physostigmine salicylate 0.16+ per cent,  $P_1$ , pilocarpine hydrochloride, 1 per cent,  $P\frac{1}{2}$ , pilocarpine hydrochloride 0.5 per cent.

Since atropine did not control the attack, an iridectomy was performed one week later. Ten days after the operation, an attack of acute congestive glaucoma occurred in the other eye, without any manifestations of iridocyclitis. The tension at first responded to miotics but later rose again, and an Elliot trephination was performed. After a La-grange sclerectomy on the right eye in 1930 and iridotaxis on the left eye in 1931, tension, with the use of miotics, became relatively normal and has remained so up to the present time. The tension curve is shown in chart 4.

In these two cases a diagnosis of secondary glaucoma was originally made, but the subsequent course has given conclusive proof that the iridocyclitis was incidental to a primary glaucoma. The iridocyclitis may have acted as a precipitating factor, or the atropine used in treating the uveitis may have made the primary glaucoma manifest. It is important to guard against a hasty diagnosis of secondary glaucoma, on the basis of a brief period of observation.

These 2 cases (cases 10 and 11), which were uncovered only in retrospect after careful analysis of their course, illustrate the pitfalls in the present day approach to the problem of the relation of glaucoma to iridocyclitis and of iridocyclitis to glaucoma.

The following classification of glaucoma associated with iridocyclitis may prove helpful.

- (1) Iridocyclitis occurring in a patient with primary glaucoma
- (2) Relatively mild cyclitis in which ocular hypertension occurs at the onset, or early in the course, of the disease
  - (a) Syndrome of recurrent glaucomatocyclitic crises
  - (b) Iridocyclitis without posterior synechias (or with old synechias) associated with the early appearance of ocular hypertension
- (3) True secondary glaucoma resulting from iridocyclitis
  - (a) Early stage, associated with plasmoid aqueous, active iridocyclitis and fresh posterior synechias
  - (b) Later stage, associated with structural changes in the filtration channels or with long-standing uveitis

Other clues which have a bearing on the over-all relation of glaucoma to iridocyclitis may be derived from a careful interpretation of the features presented by the syndrome of glaucomatocyclitic crises, since this represents a true intermediate group between the primary and the secondary glaucomas. The following features relate this syndrome to secondary glaucoma.

- 1 Strict unilaterality of the ocular hypertension over many years of observation
- 2 The presence of cells in the aqueous and keratic precipitates during, and for a short time after, most attacks
- 3 The occurrence of glaucoma in the lighter-colored eye in 3 cases with heterochromia
- 4 Lack of uniformity in response to miotics and mydriatics

The following features relate it to the primary glaucomas.

- 1 In 3 out of 6 cases, pupillographic studies showed the type of curve usually found with primary glaucoma.

2 In all 6 cases the pupillographic responses were the same in the two eyes This has been shown to be characteristic of unilateral primary glaucoma (Lowenstein and Schoenberg)

3 The attacks of ocular hypertension sometimes preceded the appearance of cyclitic signs by a day or two

4 The severity of the glaucomatous attack was out of proportion to the cyclitic manifestations

5 In 2 cases in this series primary glaucoma was present in another member of the family This ratio is in line with the percentage of cases of hereditary glaucoma found by us in a study of 400 cases of primary glaucoma<sup>8</sup>

6 Individual attacks might occur without any keratic precipitates or cells in the aqueous, although previous episodes were accompanied with these changes In this connection, we wish to report a case which puzzled not only us but other ophthalmologists as well, and which may be understood better in the light of the present concept

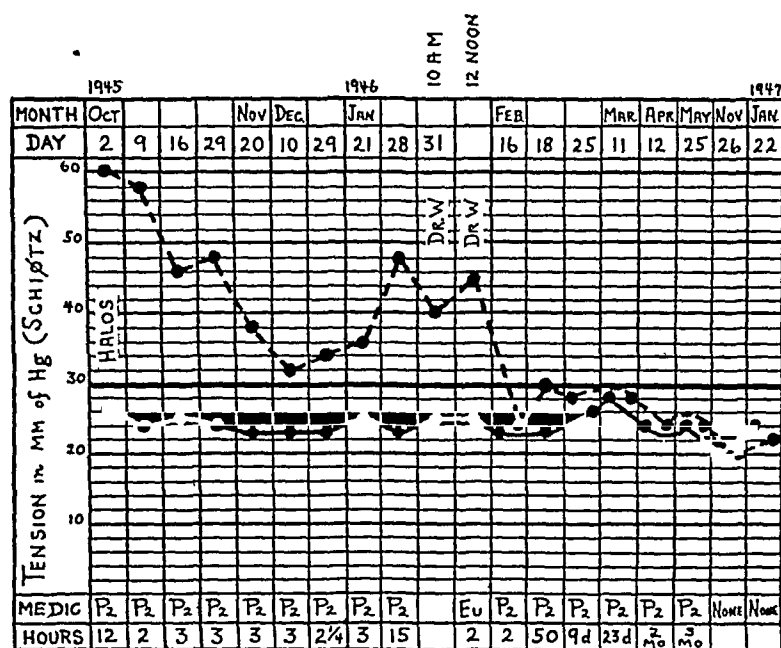


Chart 5 (case 12) —Tension curve for a patient with glaucoma (self limited) in the left eye  $P_2$  indicates pilocarpine hydrochloride, 2 per cent,  $Eu$ , eucatropine hydrochloride, 5 per cent

CASE 12—M G, a housewife aged 49, was first seen by us on Oct 2, 1945 She had had recurrent blurred vision and noted rainbows in her left eye, especially at night, for two weeks Tonometric readings were 26 mm in the right eye and 60 mm in the left eye Corrected vision was 20/30 in the right eye and 20/25 in the left eye The pupils were equal The irises were of the same color Examination with the slit lamp failed to show any cells or deposits Both anterior chambers were of normal depth, but the angles were moderately narrow In spite of the use of 2 per cent pilocarpine hydrochloride, the tension remained between 45 and 60 mm for nearly two months, after

7 Lowenstein, O, and Schoenberg, M J Pupillary Reactions of the Seemingly Unaffected Eye in Clinically Unilateral Simple Glaucoma Pupillographic Contributions to Diagnosis of Glaucoma in Preclinical Stage, Arch Ophth 31:392 (May) 1944

8 Posner, A, and Schlossman, A Development of Changes in Visual Fields Associated with Glaucoma, Arch Ophth, to be published



which it dropped to 30 mm. Vision in the right eye improved to 20/15. The fields showed no change. On November 9 the patient had, for the first time, an attack of bronchial asthma and a temperature of 99.8 F. She had a family history of allergy.

On Jan. 29, 1946, the tension rose again to 49 mm. in the left eye, and she complained of seeing a black circle and dots in the central field of that eye. Another ophthalmologist dilated her left pupil with eucatropine hydrochloride U.S.P., which raised the tension only by 5 mm. With mydriasis, a curved line surrounded by dusty opacities was seen in the vitreous adjacent to the retina in the macular zone. No focus of choroiditis was present. Surgical intervention was suggested by this, and still another, prominent ophthalmologist, the latter making the diagnosis of primary glaucoma. Operation was temporarily deferred. On Feb. 16, 1946, the tension was down to 24 mm., and the patient complained of severe, sharp pain in her eye after use of the miotic. All medication was discontinued. The pain subsided, and the tension has remained normal and equal in the eyes up to the time of this report. The opacities in the vitreous have since disappeared. Pupillographic studies on March 24, 1946, six weeks after discontinuation of miotics, revealed a bilateral curve similar to that found in cases of primary glaucoma (chart 5).

This case of self-limited unilateral glaucoma of the congestive type, which was regarded as primary at first, shows several obvious points of similarity to the syndrome of glaucomatocyclitic crises. It differs from the latter in the absence of signs of cyclitis. However, several opacities in the vitreous, which may well have been cells or clumps of cells, were observed adjacent to the retina without any visible choroiditis. These appeared during the course of the glaucoma and disappeared after subsidence of the hypertension.

Like the pathogenesis of glaucoma in general, the mechanism involved in the production of glaucomatocyclitic crises is obscure. However, we shall venture to advance a hypothesis based, to a certain extent, on established physiologic principles. It is our impression that this syndrome is engendered by a central disturbance in the hypothalamus, superimposed on a labile peripheral autonomic nervous system. The central factor is expressed by the bilaterality of the pupillographic findings (even when the curve is not the same as that found in cases of primary glaucoma) and by the association with hypertensive vascular disease, migraine and allergies, and with fever in 1 case. The peripheral factor was evidenced by the unilaterality of the disease, anisocoria, heterochromia and homolateral urticarial manifestations in 2 cases. It is possible, however, that a unilateral disease picture, such as this is, may be explained entirely on the basis of a central disturbance in the hypothalamus.

The fact that the disease in this group of cases was unilateral does not exclude the possibility, on the one hand, that certain cases of bilateral uveitis with glaucoma in which the latter is out of proportion to the former, and, on the other, some cases of glaucoma which pass as

primary only because of the absence of keratic precipitates, may also be related to this entity

Treatment should be administered cautiously. Pilocarpine hydrochloride may be used in low concentrations of 0.5 to 2 per cent. Phenylephrine hydrochloride, 10 per cent, or epinephrine bitartrate, 2 per cent, may be tried, but the patient should be under observation for a few hours. Physostigmine, neostigmine and occasionally even pilocarpine may cause acute discomfort and redness of the eye. We were loath to use di-isopropyl fluorophosphate in this group of cases. Although the drug proved extremely beneficial in some of our cases of refractory glaucoma, it gave rise to severe discomfort in a few patients of the younger group.<sup>9</sup> In a case of acute glaucoma with minimal subjective and objective signs, it is advisable to use medication cautiously until the nature of the disease becomes evident. Surgical intervention is contraindicated, since the course is not influenced by it. Paracentesis has been reported to be of value in relieving an acute attack.<sup>2</sup>

#### SUMMARY

Nine cases, forming a homogeneous group which represents a type of glaucoma intermediate between primary and secondary glaucoma, are described.

It is proposed to call this condition a syndrome of glaucomatocyclitic crises, to distinguish it from primary glaucoma, on the one hand, and secondary glaucoma, on the other.

A tentative hypothesis is advanced which relates this syndrome to a disturbance of the central and the peripheral autonomic nervous system.

Treatment should be confined to the use of low concentrations of pilocarpine hydrochloride.

A classification of glaucoma associated with iridocyclitis is presented.

667 Madison Avenue

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A few of these cases were originally those of the late Dr. Mark J. Schoenberg. His carefully kept records and detailed notes helped us greatly in the preparation of this paper.

The pupillographic studies were made by Dr. Otto Lowenstein. All tension readings refer to the 1924 Schiötz graph unless otherwise stated.

<sup>9</sup> A patient, aged 57, who is subject to recurring attacks of unilateral glaucoma without congestive or cyclitic signs, received 1 drop of di-isopropyl fluorophosphate ("DFP"). This was followed by marked reduction of tension. However, extreme discomfort, injection of the bulbar conjunctiva and pain when he attempted to read lasted for two weeks and was only temporarily relieved by homatropine.

## DISCUSSION

DR L VON SALLMANN, New York It was of great benefit to us to have Dr Posner and Dr Schlossman direct our attention to a type of unilateral glaucoma so far scarcely considered or recognized as a definite syndrome. Such recurrent attacks of increased intraocular tension with transient cellular and larger deposits on the cornea are usually considered of borderline type, and treatment is rather arbitrary, depending on the ophthalmologist's intuition. From the authors' description, it is evident that this syndrome can be fairly well distinguished from typical primary glaucoma with a few deposits on the cornea, from primary glaucoma with superimposed cyclitis unrelated to the glaucoma, from secondary cyclitic glaucoma and from the so-called sympathetic glaucoma of Streiff, with and without heterochromia.

It may not be easy to make this distinction in an isolated case, since similar signs and symptoms are common to other groups, and since, as we have learned from Posner and Schlossman's paper, close study of the course of the disease over long periods is necessary to obtain conclusive diagnostic data. However, the observations presented here, together with those in Kraupa's and a few other cases reported in the literature, round out the picture and strengthen the impression that the disease represents an entity.

Posner added to the general symptomatology of the disease the results of the pupillographic examinations and concluded from them, on the basis of Otto Lowenstein's work, that the sympathetic center in the diencephalon was involved. I must leave it to the experts in this field to evaluate and to interpret the pupillographic curves. There is no reason to doubt the correctness of this interpretation. Nevertheless, the question may be raised whether, in view of the unilaterality of the lesion, a disorder in the subordinate ciliospinal center of Budge can be completely disregarded. In 3 of Posner's cases, in 1 of Passow's cases and in several of Kraupa's series there were varying degrees of heterochromia. Heterochromia, especially complicated heterochromia, was pathogenetically related by Passow, and recently by Appel and Leo Hess, to Bremer's status dysraphicus, which is said to be due to a congenital anomaly in the cervical area of the spinal cord. I believe that the authors' cases were not examined from this neurologic standpoint.

In addition to the hypothalamic disturbance, Posner assumes the coexistence of a peripherally operating mechanism, such as a labile peripheral autonomic system, this factor must be present unilaterally. There seems to be a considerable range of alternative explanations and speculations. One could assume that the functions of the terminal nerves or the capillary motor response of other intraocular mechanisms of regulation are at fault in the one eye. In view of the presence of infective foci and the strong allergic reactions of some of the patients, the question arises whether an antigen-antibody reaction or a toxic factor could not be responsible for the onset of the periodic attacks in a disposed eye. That is, the cells in the aqueous and the precipitates on the cornea could be the expression of a transient, low grade inflammation rather than of a primarily nervous disturbance.

What further studies may reveal on the relation between disorders of the sympathetic centers and between the centers and a peripheral mechanism remains to be seen. At present, it seems likely that a transient increase in the permeability of the ciliary capillaries is the most important single peripheral factor which has a bearing on the development of the recurrent attacks. In the last year studies were conducted in the Knapp Laboratory on an experimental glaucoma induced by increased permeability of the ciliary capillaries. Various therapeutic approaches were studied on experimental animals. The effects of adrenergic drugs, of posterior pituitary injection U S P, of substances acting on the intracellular cement, such as calcium ions and adrenal cortex hormone, and of a series of histamine antagonists were tested, and promising results were obtained in respect both to the reduction of increased permeability of intraocular capillaries and the lowering of intraocular tension. There is some hope that one or another of these therapeutic measures will be of help in the glaucomatocyclitic crises described by Posner and Schlossman.

# CONGENITAL GROUPED PIGMENTATION OF THE RETINA

Report of Two Cases

PAUL TOWER, M D

LOS ANGELES

Congenital grouped pigmentation of the retina is a rarely encountered condition, Stephenson<sup>1</sup> found only 3 instances of this anomaly in a series of 2,400 examinations, while Blake<sup>2</sup> noted not more than 7 cases of this kind in twelve years of ophthalmologic practice. The clinical picture of grouped pigmentation, as well as the characteristic features distinguishing it from abnormal multiplication due to a progressive pathologic process, were excellently described by Stephenson.

The changes which occupy a sector-like portion of the fundus, consist of groups made up of black to dark chocolate brown spots, which, as seen by the direct method, range in size from 0.5 to 2 mm, or more, in general terms it may be said that the farther away the spots lie from the optic disk the larger they become.

This specific hyperplasia of the pigmented cells of the retina is listed in the literature under various names: congenital pigmentation of the retina, melanosis retinae and congenital pigmented plaques of the retina. The term "nevroid pigmentation of the fundus," which is also sometimes used, is misleading, as nevroid cells have never been encountered in this condition.

Illustrations of grouped pigmentation of the retina were published as early as 1868, yet the true character of this anomaly was not recognized at that time, and the condition was erroneously described as an unusual form of progressive pigmentary degeneration, similar in many respects to retinitis pigmentosa. While most of the ophthalmologic textbooks fail to mention grouped pigmentation of the retina, an example appears in Bedell's<sup>3</sup> atlas of photographs of the fundus oculi (1929), in that case, a group of four round spots of retinal pigment can be discerned beneath one of the radicles of the temporal branch of the inferior

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1 Stephenson, S. A Peculiar Form of Retinal Pigmentation, *Tr Ophth Soc U Kingdom* 11 77, 1891.

2 Blake, E. M. Congenital Grouped Pigmentation of the Retina, *Tr Am Ophth Soc*, 1926, p. 223.

3 Bedell, A. J. Photographs of the Fundus Oculi. A Photographic Study of Normal and Pathological Changes Seen with the Ophthalmoscope, Philadelphia F. A. Davis Company, 1929, vol. 2, p. 274.

portion of the vena centralis retinae. The patient's vision in this eye was reported as 20/20. Three cases were described by Mann<sup>4</sup> in 1932. The single case reported by Perera<sup>5</sup> in 1939 is accompanied with a photograph presenting the arrangement of pigment which is typical of this condition, as well as with a description of the characteristic signs of grouped pigmentation. The necessity of careful differentiation of this anomaly and pigmentation due to hemorrhage, or other pathologic processes was stressed by Casanovas,<sup>6</sup> in commenting on an additional case in 1945.

Little is known about the pathologic process in grouped pigmentation. No satisfactory explanation appears to have been given for the typical feature of this anomaly—the appearance of dark spots in a characteristic arrangement within certain segments of the retina, as distinguished from the continuous layer of normal coloring matter encountered in the inner portion of the hexagonal columnar epithelial cells forming the stratum pigmenti retinae. Collins and Mayou<sup>7</sup> gave a brief description of grouped pigmentation on the basis of microscopic observations. Sir Herbert Parsons,<sup>8</sup> in an earlier pathologic study, encountered within the retina a number of deeply pigmented epithelial cells. Some of these were surrounded by nodules of hyaline matter, closely resembling the transparent substance of the lamina basalis of the choroid. He assumed that the anomaly of grouped pigmentation could be traced to irregularities in the evolution of the two layers of the retina within the secondary optic vesicle. Whenever rods and cones fail to develop in Jacob's membrane, empty spaces occur into which the pigmented epithelial cells of the outer stratum will migrate. Collections of such supernumerary cells containing a deposit of coloring matter produce the typical plaques of congenital grouped pigmentation. Ida Mann<sup>9</sup> stated that this developmental abnormality may be caused by an atypical process in the differentiation of the optic cup during the embryonic stage. Either irregular chromatosis may occur within groups of plastids in the inner stratum, or the outer stratum, which normally persists as a single cellular layer, may undergo localized proliferation.

4 Mann, W. A. Grouped Pigmentation of the Retina, *Arch Ophth* 8 66 (July) 1932.

5 Perera, C. A. Congenital Grouped Pigmentation of the Retina *Arch Ophth* 21 108 (Jan) 1939.

6 Casanovas, J. Grouped Pigmentation of the Retina, *Arch Soc oftal hispano-am* 5 129 (Feb) 1945.

7 Collins, E. T., and Mayou, M. S. *Pathology and Bacteriology of the Eye*, ed 2, Philadelphia, P. Blakiston's Son & Co., 1925, p 27.

8 Parsons, J. H. Anomalies of Pigmentation, *Tr Cong internat d'opht*, 1904, p 152.

9 Mann, I. *Developmental Abnormalities of the Eye*, New York, The Macmillan Company, 1937, pp 153-154.

Two cases of grouped pigmentation of the retina are reported, one of which appears to be of special interest, as the observations in this instance may permit certain conclusions relative to the developmental mechanism responsible for this rare anomaly

#### REPORT OF CASES

CASE 1—H F, a white woman aged 30, was referred because of a suspected pathologic condition of the fundus. Inspection of the exterior of the eyes failed to reveal any significant data. Refraction demonstrated bilateral visual acuity of 20/20, without correction. Vision in the fields peripheral to the point of fixation was normal bilaterally, and no scotomas occurred in the center of the visual field. On ophthalmoscopic examination, both fundi presented a somewhat tassellated appearance, but the arteries were normal, and the optic disk was well defined in both eyes. In the right fundus, in a sector of the nasal half of the retina, several groups



Fig 1 (case 1) —The fundus of the right eye is marked by groups of pigmented spots occupying an area nasal to the disk

of pigmented spots, slightly varying in size and shape, but all of dark gray color were encountered (fig 1). These patches occupied a position which, even though it was deeper than the pigmented layer of the retina, appeared to be above the inner surface of the choroid. Otherwise, the fundus of the right eye was normal. No chromatism was found in the fundus of the left eye.

CASE 2—M M, a white boy aged 12 years, was examined for correction of refractive errors. Inspection of the exterior of the eyes failed to reveal any significant data. Refraction demonstrated the visual acuity as 20/20 with a correction of  $+0.50$  cyl, axis 175, for the right eye, and  $+0.50$  cyl, axis 180, for the left eye. Vision in the fields peripheral to the point of fixation was normal bilaterally, and no scotomas occurred in the center of the visual field. No muscular insufficiency was encountered, and the media were clear. Ophthalmoscopic study revealed numerous pigmented spots in the lower portion of the retina of the right eye (fig 2). These patches of a chocolate brown color were arranged in groups, but larger spots were encountered at the periphery than close to the optic disk. In the lower portion of

the left retina, there appeared pigmented spots of a color similar to that in the right eye. But in the left fundus the patches were more numerous and larger, they were also assembled into groups, and those at the periphery were much more extended than those closer to the optic disk. On this side, however, the typical arrangement of these spots into only one sector of the retina was still more obvious (fig 2B). Bilaterally, the patches occupied a position which, even though deeper

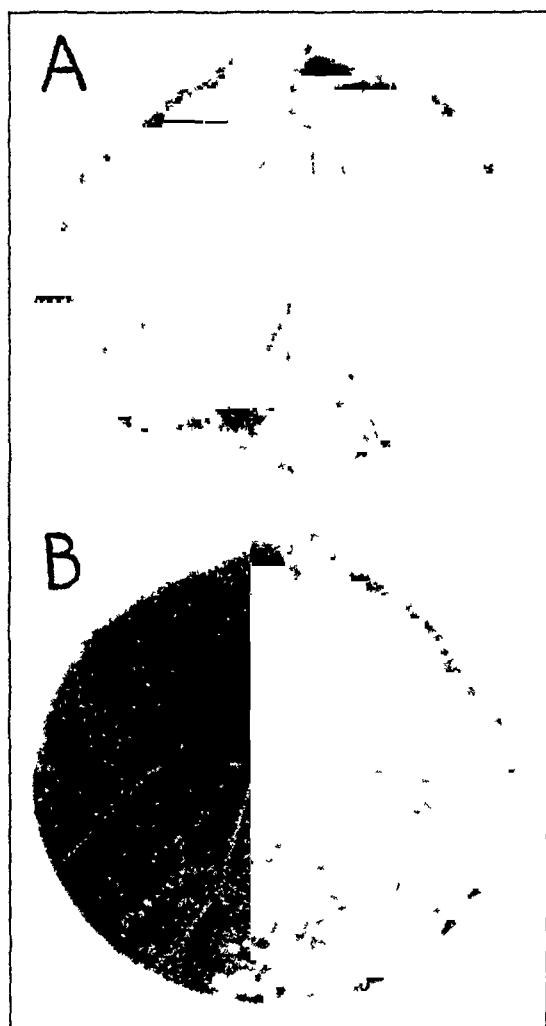


Fig 2 (case 2) —(A) The fundus of the right eye is marked by pigment deposits occupying the lower portion of the retina. (B) The fundus of the left eye is marked by pigmented plaques characteristically arranged in a triangular sector of the lower portion of the retina.

than the pigmented layer of the retina, appeared to remain above the inner surface of the choroid.

#### COMMENT

The similarities between these 2 typical cases of grouped pigmentation are clearly evident, even though in the first instance the involvement was only unilateral and the pigmented spots were neither as frequent nor as dark as in the second case. The family history failed to reveal the appearance of any comparable condition within the family of either patient,



nor was there any evidence of consanguinity. There seems to exist, therefore, no valid foundation for an assumption of the hereditary origin of this rare anomaly. It is of note, furthermore, that neither of the patients presented deformities in any other part of the body.

The diagnosis of grouped pigmentation should be based on the following pathognomonic symptoms: no defect in vision referable to the condition, and normal visual fields. The pigmented patches are typically grouped within one triangular sector of the retina, this arrangement may be more or less clearly apparent in the individual case. Only in rare instances will the area marked by chromatism extend to include the macula lutea. Generally, the pigmented deposits can be identified as situated at a deeper level than the retinal structures, but still distinguishably above the lamina basalis of the choroid. No evidence of further congenital anomalies is encountered in patients presenting grouped pigmentation of the retina, and rarely, if ever, will a similar condition be detected among other members of the patient's family. Congenital grouped pigmentation is, finally, not progressive.

Even though other pathologic processes affecting the fundus of the eye may at first glance seem to produce a similar appearance on the retina, the differential diagnosis of grouped pigmentation should not prove difficult on the basis of the enumerated signs.

Of the 2 cases reported here, the second would appear to be of particular interest. In this case, the arrangement of the groups of pigmented spots in a single sector in the lower portion of the retina—the apex of which points toward the disk, or is identical with it—becomes clearly evident. Yet this triangular region of the retina to which the anomaly of grouped pigmentation seems to be restricted in typical cases corresponds closely to the zone of the choroid to which the occurrence of coloboma is usually limited. It is not intended to enter into a detailed discussion of coloboma at this point. But the obvious similarity of the area of involvement in the two developmental abnormalities may possibly indicate a deeper than merely topographic relation between grouped pigmentation of the retina and coloboma of the choroid.

Coloboma can be traced to the persistence of the choroidal fissure of the optic cup and the optic stalk, which usually closes during the seventh week of fetal life. Coloboma of the choroid frequently produces scotoma of the retina, a condition which is rarely, if ever, concomitant with grouped pigmentation. But if Parsons's<sup>8</sup> hypothesis of the probable cause of congenital grouped pigmentation is accepted and the development of supernumerary deposits of coloring matter is traced to a localized defect in the development of the layer of rods and cones, then the topographic analogy between the congenital anomalies of grouped pigmentation of the retina and coloboma suggest a similar etiologic factor in the two conditions. Conceivably, the anomalous accumulation of pigment in Jacob's

membrane may be due to an irregularity in the occlusion of the choroidal fissure, different, of course, from that leading to coloboma. Or, on the other hand, some other pathologic process during the patency of this fetal cleft may result in a disturbance of the development of the different strata of the retina. At present, no additional evidence is available which would help in substantiating this theory of the possible causes responsible for the occurrence of grouped pigmentation of the retina. Yet the localization of the pigmentary deposits in a specific sector of the fundus, so clearly evident in the second case presented here, is a factor which should be taken into consideration in any future study of the cause of this congenital anomaly.

#### SUMMARY

Two cases of congenital grouped pigmentation of the retina are presented.

The literature on this congenital anomaly, especially that relating to its pathology, is reviewed.

The necessity of differential diagnosis from other conditions affecting the fundus of the eye is stressed.

The typical arrangement of the deposits of coloring matter in a triangular sector of the inferior portion of the retina suggests that this anomaly may have a cause similar to that of coloboma of the choroid, and that it may be possible to trace it to irregularities in the closure of the choroidal fissure.

610 South Broadway (14)

# CRESCENTIC DEFORMITIES OF THE LID MARGIN

SIDNEY A. FOX, M D

NEW YORK

Crescentic (lunate) dehiscences of the lid margin are deformities in which there is absence of an appreciable portion of the border of the lid, but the lesion is shallow and rarely extends beyond the tarsus. Although the loss of tissue is not great, the deformity is usually unsightly and, if the upper lid is involved, leaves a large area of cornea exposed (fig 2A). While reconstruction of this defect does not present a major problem, careful handling is required to get a good cosmetic result. Of several methods tried, the technic to be described was found to be the simplest and to yield the best results in a series of 14 cases. Photographs from an illustrative case are presented (fig 2).

## TECHNIC

The involved portion of the lid is split into a skin-muscle and a tarsoconjunctival layer, the dissection being made sufficiently wide to mobilize both layers thoroughly. All scar tissue is carefully resected. The opposing lid edge is freshened and also split into its two layers, but only to a depth of about 2 mm (fig 1A, broken lines). The tarsoconjunctival layers of the two lids are united by a 00000 braided black silk (running) suture, anchored at both ends. The skin-muscle layer of the injured lid will now retract, leaving an area of raw tarsal surface exposed (fig 1B). If necessary, a mattress suture is passed through the uninvolved portion of the lid margins to immobilize them (fig 1B).

A free graft, cut to pattern, is then taken from the brow. This includes about 4 mm of brow hair to replace the lost cilia of the lid margin and some clear skin to make up for the rest of the lost cutaneous tissue of the lid (fig 1B, broken oval). This graft should be cut about a third larger than the recipient site to allow for shrinkage. The graft is sewed into place with 00000 braided black silk interrupted sutures. The donor site is closed with 0000 mild chromic surgical gut subcuticula sutures and 0000 braided black silk skin sutures (figs 1C and 2B). The site of operation is covered with perforated oiled silk or "cilkloid" and a firm pressure dressing applied. It is not necessary to patch the fellow eye. The dressing is removed on the seventh day, the area is cleansed, the brow sutures are removed, and the pressure dressing is reapplied for five days longer. By this time the graft has "taken," and the sutures are removed. The eye is patched daily for a few more days until healing is complete, at which time dressings are discontinued. The lids are separated four weeks later and the edges are allowed to epithelize. The lid will be somewhat thickened for a month or so and will then assume a normal appearance. Cilia should begin to reappear six to eight weeks after operation (fig 2C).

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From the Department of Ophthalmology, New York University School of Medicine

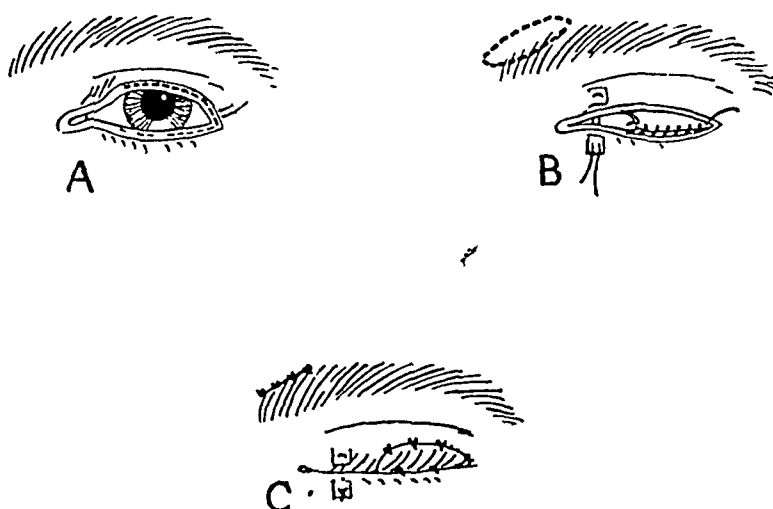


Fig 1—Technic of repair of crescentic deformity of the lid margin See text for explanation

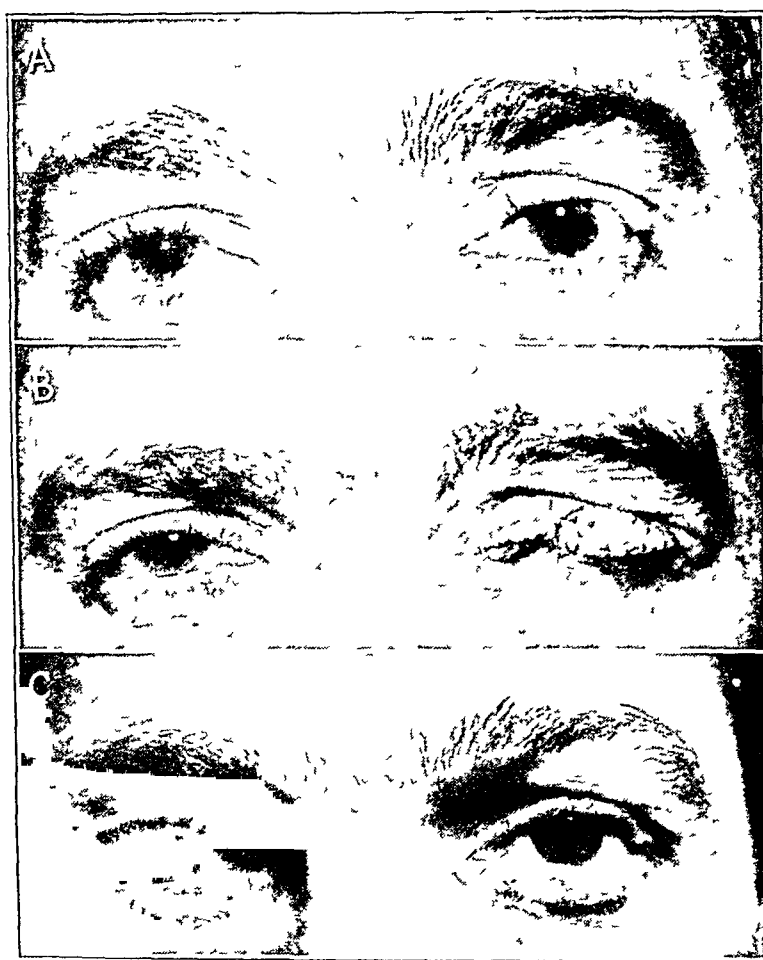


Fig 2—*A*, crescentic dehiscence of the left upper lid, with abnormal exposure of the cornea, *B*, one week after repair, with donor site healed and graft "taking" well, *C*, ten weeks after repair, with the corneas showing equal exposure Note the normal lid line and good growth of transplanted lashes The donor site is well covered

## COMMENT

In another communication,<sup>1</sup> a method of repairing these lunate marginal deformities was described. This involved two stages: (a) reconstruction of the lid margin and (b) lash grafting, at a later stage. The method proposed here is preferable, for several reasons:

- 1 The patient is subjected to only one operative procedure.
- 2 Less surgical intervention means less scarring and therefore a better cosmetic result.
- 3 It is believed that this type of lash graft is more certain to "take" than the usual 3 mm. wide, hair-bearing graft planted in a trough near the lid margin.
- 4 The lash graft is closer to the lid margin and hence gives a more natural appearance.

In taking these grafts, it is probably preferable to use tissue from the lower part of the brow and the skin below it, for this matches the skin of the lid more closely in color and texture. If the socket had been anophthalmic in the case presented here, the graft would have been taken from the lower part of the left eyebrow and the skin below it. However, in that case the direction of the transplanted lashes would have been down and nasal. While this does not matter in an anophthalmic orbit, the normal eye might have been subjected to some trichiasis, since it is difficult to change the direction of hair growth. Hence, the graft was taken as shown.

Skin from above the brow is thicker and somewhat paler than the skin below the brow. But while it is a trifle more difficult to handle, experience shows that the "take" is as certain, and after several weeks the cosmetic result is about as good.

## SUMMARY

A method of simultaneous lash grafting and reconstruction of crescentic deformities of the lid margin is presented.

63 East Seventy-Fifth Street (21)

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1 Fox, S. A. Some Methods of Lid Repair and Reconstruction, *Am J Ophth* 29:452 (April) 1946.

Mr. Herbert M. Kraus assisted in drawings of the technic.

## COTTON SUTURES IN OPHTHALMIC SURGERY

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ROCHESTER, MINN

During the past seven years several reports<sup>1</sup> concerning the use of cotton thread as a suture material have appeared in the literature. These reports were made by general surgeons and were based on the use of cotton sutures in more than 3,000 cases. In most instances the general surgeons were favorably impressed with the use of cotton for suturing certain types of wounds. No reports on the use of cotton as a suture material in clinical ophthalmology were made in a similar seven-year period. Berens and Romaine<sup>2</sup> included cotton thread in their report on the comparative value of sutures employed in surgical procedures on the extraocular muscles, but their experimental work was carried out on rabbits. In the military service I used cotton as a suture material in approximately 50 operations on the eye. It seems to possess features that make it applicable to certain types of ophthalmic surgery.

Cotton fiber, a cellulose material, has a natural twist which facilitates its being spun into thread. Because of this natural twist of the individual cotton fiber, the finished thread is very compact in structure. Fraying of cotton thread is negligible, and the natural twist facilitates the tying of a knot. In spite of its compactness, cotton thread still possesses a high

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From the Section on Ophthalmology, the Mayo Clinic

Read at the meeting of the Minnesota Academy of Ophthalmology and Otolaryngology, Rochester, Minn., May 16, 1947

1 (a) Meade, W. H., and Ochsner, A. The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Material, *Surgery* **7** 485-514 (April) 1940. (b) Meade, W. H., and Long, C. H. The Use of Cotton as a Suture Material, with Particular Reference to Its Clinical Application, *J. A. M. A.* **117** 2140-2143 (Dec. 20) 1941. (c) Thorek, P. Five Years' Experience with Spool Cotton as Suture Material. Routine Use in over One Thousand Operations, *Am. J. Surg.* **71** 652-656 (May) 1946. (d) Kanne, W. P., and Smith, W. E. Clinical Observations on the Use of Cotton as a Suture Material, *Ohio State M. J.* **41** 625-627 (July) 1945. (e) Floyd, J. R., and Brockbank, M. J. Spool Cotton as Suture Material, *Surgery* **16** 403-406 (Sept.) 1944. (f) Hyde, T. L. Cotton Surgical Suture Material, *ibid.* **16** 407-415 (Sept.) 1944.

2 Berens, C., and Romaine, H. H. A Comparative Study of Sutures Employed in Surgery of the Extraocular Muscles, *Am. J. Ophth.* **29** 1126-1134 (Sept.) 1946.

friction coefficient, so that a knot or hitch shows no tendency to slip even though the ends of the thread are cut short. From the standpoint of the ease with which it can be tied, the absence of slipping and the smallness of the resulting knot, cotton thread is preferable to chromic surgical gut, plain surgical gut or silk.

Commercially, cotton thread is often treated with chemicals in order to increase its tensile strength. Mercerized cotton is thread that has been immersed in sodium hydroxide. Quilting cotton is thread that has been immersed in starch. Spool cotton, or ordinary sewing cotton, has little or no chemical impregnated in the thread. The irritating effect of chemically treated cotton on body tissues has not been determined experimentally, but clinically mercerized and quilting cotton do not seem to possess distinct advantages over spool cotton. The tensile strength of spool cotton is increased from 10 to 15 per cent<sup>1a b</sup> by wet sterilization, whereas the tensile strength of silk is<sup>1b f</sup> decreased by similar sterilization. Berens and Romaine<sup>2</sup> estimated the tensile strength of a strand of 000 cotton to be between 2 and 3 pounds (0.9 and 1.3 Kg.). This tensile strength of cotton is about equal to that of chromic surgical gut, a little greater than that of silk and about twice as great as that of plain surgical gut, when similar-sized threads are compared. From the standpoint of tensile strength, cotton thread compares well with other suture material.

Cotton is a relatively inert substance, as judged by the response of the body tissue to its presence. The natural twist of the cotton fiber and the compactness of the finished thread make the suture almost impervious to infiltration with cells or body fluids, so that the tensile strength of the suture is preserved. This feature is in striking contrast to the behavior of surgical gut, in which the suture is weakened in direct proportion to the fluid it absorbs and the cellular reaction that it incites. Even silk tends to fray and lose its tensile strength because of the tendency of cellular elements to migrate along the individual strands and of fluid to reach the center of the thread. This feature of cotton makes it the suture material of choice in the presence of infected wounds according to reports<sup>1a c</sup> in the literature.

The tissue reaction that is incited by cotton consists in fibroblastic proliferation and a slight lymphocytic response. The fibroblastic response, and, in reality, healing, occur earlier with cotton than with silk or surgical gut<sup>1a</sup>. The fibroblasts and lymphocytes seem to engulf the cotton suture and, in the initial phases of wound healing, surround the cotton thread like a cuff<sup>2</sup>. Berens and Romaine<sup>2</sup> performed recessions and resections with cotton sutures on the eyes of a series of rabbits and made microscopic studies of wound healing at intervals of twenty, forty and sixty days after operation. Twenty days after operation they noted the fibroblastic cuff around the suture. Forty days after operation they observed "fibrous tissue replacement of suture." At the end of sixty days they noted fibrous

tissue but no evidence of the suture. Because cotton has been considered to belong to the nonabsorbable group of suture materials, it has rightly been considered to possess the danger of any retained foreign body, but, in view of the studies of Berens and Romaine,<sup>2</sup> perhaps it should be thought of as "relatively nonabsorbable." In 1 instance I had the opportunity to dissect an eye in which I had buried a cotton suture in the sclera near the limbus about four months previously. Grossly, I was unable to find the cotton suture. Even though the suture is a potential foreign body for at least a portion of the postoperative period, this disadvantage is somewhat modified by the minimal tissue response that is incited by cotton. Meade and Ochsner<sup>1</sup> favored cotton over any other suture material from the standpoint of the least postoperative reaction of tissue and the earliest healing. With their statement I agree.

I first used cotton as a suture material in the so-called Mules-Dimitry operation, in which some type of implant is inserted into the scleral shell. This operation is often followed by intense postoperative edema, slippage or sloughing of the buried suture, gaping of the edges of the scleral wound and ultimate extrusion of the implant. With cotton sutures, I found there were less postoperative edema, no extrusion of the implant and earlier healing than with surgical gut or silk.

Next, I tried cotton sutures in the repair of wounds of the eyelids and margins of the eyelids. Where the wound had produced a defect in the margin of the eyelid and considerable loss of tissue substance, I inserted cotton sutures in the tarsal plate and was able to coapt the edges of the wound, even under considerable tension. With silk sutures there seemed to be a greater tendency of the suture line in the tarsus to spread. With surgical gut, infection and sloughing of the tarsus were common. Where it was necessary to repair a defect in the eyelid with some type of sliding flap, cotton sutures were placed in the subcutaneous tissues. This measure assured adequate tension and made it possible to insert fewer sutures in the superficial portion of the skin.

In recessions with scleral fixation and in resections on the extraocular muscles, I have used cotton sutures without complications. In these operations, the cotton sutures were buried and the overlying conjunctiva was closed with silk. The postoperative tissue reaction was less, the patients became ambulatory sooner, and muscle exercises could be started earlier than after similar operations in which surgical gut sutures were employed.

In dacryocystorhinostomy procedures I have utilized cotton thread for sewing the mucosa of the lacrimal sac to the nasal mucous membrane. I have not found that cotton is of any particular advantage over other types of suture material in the average case in which this operation is required. Theoretically, cotton might have advantages over other suture material in those cases in which purulent dacryocystitis has occurred.



previously or in which gross contamination of the operative wound is likely

In perforating wounds of the globe involving the region of the limbus and ciliary body, I have inserted cotton sutures in the sclera to prevent gaping. The inertness of the cotton fiber and the small knots that are possible would seem to recommend the cotton suture for these occasions.

I have had no experience with the use of cotton sutures in cataract operations or in the so-called tucking operations on the extraocular muscles. In some of the operative procedures designed for the correction of ptosis, cotton sutures might be used. I think this suture material might also be utilized in the muscle transplantations for paralytic strabismus.

In practically all cases in which I have used cotton, I have inserted it as an interrupted suture and have allowed it to remain in the tissues. For closure of surface wounds, I feel that black silk is preferable to cotton because it is more visible and more easily removed.

The ordinary commercial spool cotton in sizes 60 and 80 seems applicable to the demands of ocular surgery. Number 60 cotton thread is comparable in diameter to 0000 surgical gut U S P. Since manufacture of spool cotton is not well standardized, thread of similar diameters obtained from different sources will vary in tensile strength.

Since I was accustomed to using silk and surgical gut, I found cotton hard to work with at first. It is very limp, and it tends to stick to all objects and tissues in the operative field. It is not elastic, and it will break readily if tension is too rapidly placed on the thread during the tying of the knot. This is its chief disadvantage. One should be careful not to use too large a thread, for the suture will probably slough. One should remember that it has a high tensile strength, so that a small diameter of thread is sufficient.

#### SUMMARY

Cotton fiber is an inert material with a natural twist which can be tied into small, stable knots with a high tensile strength, yet incites early healing but with little undesirable tissue response. These characteristics are features that might be considered in the possible use of cotton as a suture material in ophthalmic surgery.

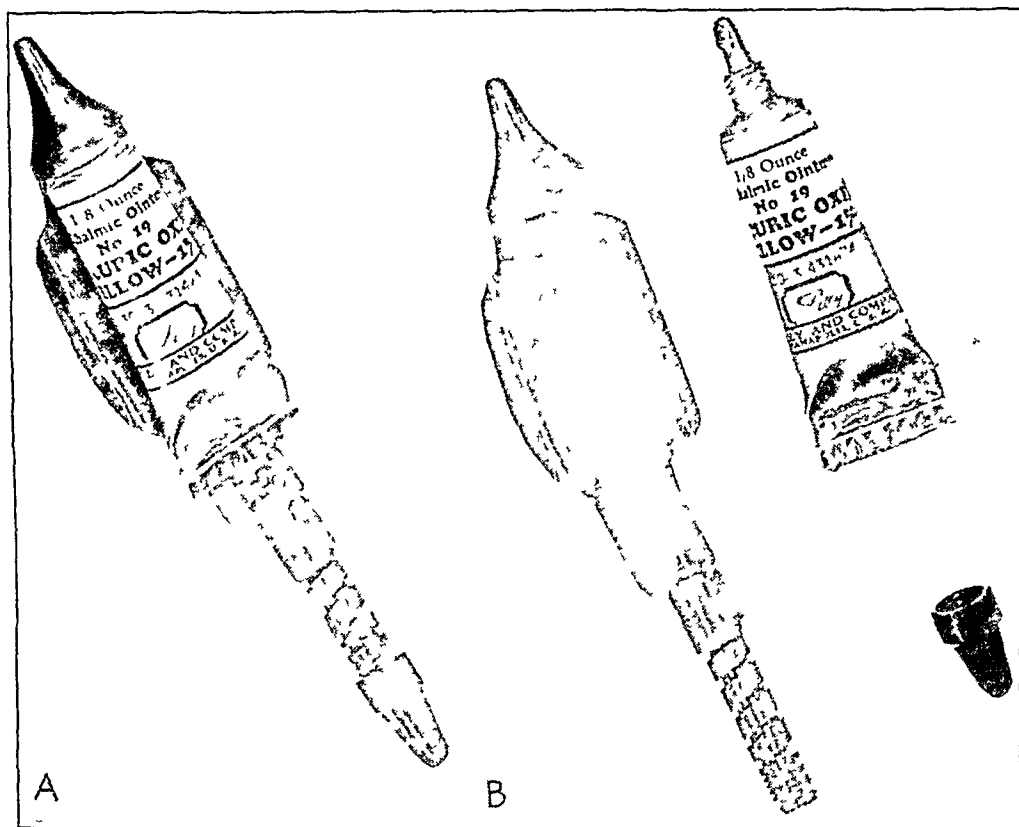
The Mayo Clinic

# Clinical Notes

## EYE OINTMENT DISPENSER

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The danger of contamination from the tips of ointment tubes has long been recognized, and several substitute methods have been employed. None of these methods, however, has proved entirely satisfactory, and for this reason the metal container shown in the illustration was devised.



A, eye ointment dispenser with tube in position. The tube cap has been screwed on the end of the ointment dispenser. B, tube and cap of ointment dispenser.

Sterile glass or plastic rods for the application of ointment to eyes have two distinct disadvantages. 1 The method is cumbersome because of the changes in the viscosity of the ointment. During the summer months scarcely any ointment will adhere to the glass rod, while in the winter months and at cold temperatures too much ointment adheres to the rod. 2 The use of glass rods may be traumatizing to the sensitive eye.

Sterilization of the tubes is not practical, especially in office practice and in wards, where they must be resterilized after each application.

A metal nozzle or glass tip screwed onto the tube is difficult to handle, and the inside of the cap may become contaminated while the ointment is being applied. The metal container answers all these objections, for the following reasons. 1 Each metal container is completely sterile. 2 No

part of the tube comes in contact with the patient's eye 3 A separate sterile container is used for every patient 4 There is no danger of contaminating the inside of the cap, as it is screwed onto the end of the sterile adjustment rod while the tube is in use 5 The same tube may be used over and over again until all of its contents has been used up 6 The tubes may be set up in a battery of a dozen or more containers before a series of dressings are done 7 The containers fit several of the standard-sized ointment tubes and may be sterilized indefinitely, so that the cost of the dispenser is well offset by its practical applicability

The dispenser may be obtained from the Werner Surgical Supply Co, 1060 Lexington Avenue, New York

927 Park Avenue

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### THE "INCIDENT NEUTRAL" POINT IN RETINOSCOPY

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When one speaks of the neutral point in retinoscopy, one ordinarily refers to the point where the emergent rays from the patient's eye meet This may be called the "emergent neutral" point But there is another neutral point which concerns the incident light and may be called the "incident neutral" point The latter neutral point is obtained when one uses a concave mirror (or a concave mirror effect) of intermediate focus When the incident light is made to focus in the plane of the patient's pupil, there will be neutrality of motion irrespective of any refractive error the patient may have

One can understand this phenomenon from the basic facts in retinoscopy, without elaborate tracings of rays A plane or a long focus concave mirror always produces a "with" movement of the light patch on the patient's retina, although it may sometimes appear to move "against" A short focus concave mirror always produces an "against" movement of the light patch on the patient's retina, although this, too, may sometimes appear to move "with" One would expect, therefore, that a concave mirror of intermediate focus such as to bring the incident rays to a focus in the plane of the patient's pupil would produce no movement of the light patch on the patient's retina, irrespective of any refractive error the patient might have

A simple way to demonstrate this is by the use of some of the modern luminous retinoscopes, with which the light source can be moved nearer to or farther away from the mirror One can thus, by continuous sliding of the light source, obtain the effect of a plane mirror or of a concave mirror of different focal lengths—long, intermediate and short Using such a retinoscope, say, on an emmetropic eye and starting with the plane mirror effect, the examiner will note a "with" movement of the reflex By sliding the light to get a concave mirror effect, he will continue to get a "with" movement until at some stage the movement ceases—and he gets neutrality By further sliding the light source, he will observe an "against" movement of the reflex He will thus get reversal of motion in the patient's eye without the interposition of lenses, simply by altering the vergence of the incident rays

Since movements of the reflex as the physician sees them are occasioned by movements of the light patch on the patient's retina, when there is no movement of the light patch there will be no apparent movement of the reflex. The examiner who unwittingly gets the incident neutral point will see the same retinoscopic phenomena as when he gets the emergent neutral point, though the latter, the really important neutral point for determining the refractive error, may be far off. With an instrument with which concave mirror effects are easily obtained, this is especially likely to happen, as I have seen, to the utter confusion of the physician, who was unaware of the existence of the incident neutral point.

These two neutral points have been called by Professor Marquez the first and second neutral points. But the terms incident neutral and emergent neutral points emphasize more fully their causation and significance. The incident neutral point is caused by the incident light having a certain vergence with reference to the patient, and the emergent neutral point, by the emergent light having a certain vergence with reference to the examiner.

## Correspondence

### CHRONIC TEARING

*To the Editor* —During the past few months following the publication of my article, "Chronic Tearing Cured by Reestablishment of Normal Tear Conduction Passages," in the December 1947 issue of the ARCHIVES, page 775, I have received a number of requests for more detailed information on the use of indwelling horsehair in maintaining the patency of the newly formed punctum and lower canaliculus. Most of these questions are concerned with what precaution need be taken so that the free end of the horsehair at the punctum does not damage the cornea by scratching or by irritating the globe.

I believe it worth while to publish the method that I have been using to obviate this danger since I submitted my article in October 1946.

Should the punctum, as well as the lower canaliculus, be closed by scar tissue, I proceed as follows. The point selected for starting the perforation into the tear sac should be slightly closer to the globe than the site of the original punctum. Comparison with the position of the punctum of the other eye (if normal) aids in correctly selecting the proper point. With the use of local anesthesia, a sharp needle on a holder is pushed through the scar tissue in the direction of the middle of the tear sac until it comes into contact with the bony lacrimal fossa. The lower lid is pulled away from the direction of the needle during the perforating. The needle is then slowly withdrawn to the point of entrance. The direction of the needle is now reversed, and a 3 to 4 mm. counterpuncture is made in the lower lid. This counterpuncture forms a blind pocket, into which the free end of the horsehair is inserted. Increasingly larger, dull-pointed needles, up to the caliber of a no. 6 Bowman probe, are used to dilate the puncture. The direction of this counterpuncture is somewhat backward and downward, being determined by the junction of the inner angle of the bony socket of the eye and the root of the nose. Immediately on withdrawal of the largest dilating needle, the horsehair is inserted as far as possible into the newly formed lower canaliculus. If the horsehair does not seem to have entered deeply enough, it is withdrawn. The dilation is repeated, and a new, stiff piece of horsehair is immediately inserted. A tiny bead is now strung on the horsehair and slid along until it is in contact with the newly formed punctum. This bead maintains the patency of the punctum. The free end of the horsehair is cut so that it fits snugly into the blind pocket prepared for it. After a period of two to three weeks, depending on the individual case, epithelization is complete, and the horsehair with its bead is removed.

Preferable to the use of a bead which slides easily on the horsehair is one that fits tightly, because it better maintains its position at the punctum. Such a bead is prepared as follows. A drop of viscous, liquid "cellophane" is allowed to dry on the horsehair, while it is revolved in all directions to secure roundness. After several days, when the drop is thoroughly dried, the tapering ends are cut off with a glass-cutting steel.

file Rough edges are smoothed with a steel nail file Such a bead can be slid with some resistance anywhere along the horsehair

It is possible that sensitivity to horsehair and/or the bead may cause irritation in allergic persons, however, I have not encountered this.

D J MORGENSTERN, M D , Brooklyn

433 Eastern Parkway

#### EFFECT OF LOCALLY APPLIED ANTIHISTAMINE DRUGS ON NORMAL EYES

*To the Editor* —Since there has been some interest in the use of the antihistamine drugs locally in the eye, the following data on the ocular tolerance to a group of these compounds, which are reported to have particularly high antihistamine activity, may be of use to persons contemplating therapeutic trials

The approximate maximum concentrations at which no alteration of the rabbit cornea occurs, as shown by examination with the slit lamp, after application of a single drop of solution are phenazoline hydrochloride ("antistin hydrochloride," Ciba Pharmaceutical Products, Inc ), 1.5 per cent, diphenhydramine hydrochloride ("benadryl hydrochloride," Parke, Davis & Company), 1 per cent, doxylamine succinate ("decapryn," Wm S Merrell Company), 5 per cent, thenylpyramine hydrochloride ("histadyl," Eli Lilly & Co ), 5 per cent, pyranisamine maleate ("neoantergan," Merck & Co , Inc ), 5 per cent, tripeleennamine hydrochloride ("pyribenzamine hydrochloride," Ciba Pharmaceutical Products, Inc ), 2.5 per cent, thenylpyramine hydrochloride ("thenylene," Abbott Laboratories), 5 per cent, phenindamine tartrate ("thephorin," Hoffmann-LaRoche, Inc ), 1 per cent At slightly higher concentrations these drugs produce temporary keratitis epithelialis At still higher concentration corneal edema develops, and there may be loss of epithelium

The maximum concentrations which are noninjurious to the rabbit cornea cannot be employed in treatment of human eyes because of production of considerable pain Concentrations which produce approximately the same discomfort as 0.5 per cent tetracaine ("pontocaine") hydrochloride in human eyes, and which might therefore, be considered the maximum dose suitable for clinical use are "antistin," 0.75 per cent "benadryl hydrochloride," 0.5 per cent, "decapryn," 1 per cent, "thenylene," 0.4 per cent, "histadyl," 0.75 per cent, "neoantergan," 0.5 per cent, "pyribenzamine," 0.5 per cent, and "thephorin," 0.5 per cent These values are for solution in 0.9 per cent solution of sodium chloride, with resultant  $pH$  ranging from 5 to 7, with the exception of that for phenindamine tartrate ("thephorin"), which is 3.5 Considerably more concentrated unbuffered solutions of these compounds have nearly the same values of  $pH$  If these solutions are adjusted to a  $pH$  of 9, all give a considerable precipitate except for "decapryn" and "antistine," both of which produce the same ocular reaction as at  $pH$  5 When they are adjusted to  $pH$  8, their effect in normal human eyes does not differ from that of the unbuffered solutions It appears that discomfort is not attributable to excessive acidity or alkalinity No perceptible injury is produced at the concentrations noted as suitable for human eyes, but there is in all instances a slight transient conjunctival hyperemia Only diphenhy-

dramine hydrochloride ("benadryl hydrochloride") has a noticeable mydriatic or cycloplegic effect, and none of the drugs produces noteworthy anesthesia on single application

No attempt has been made here to assess the penetrative characteristics or relative therapeutic values of these compounds, which, of course, would be determined by many factors in addition to the small differences in local toxicity which have been noted here

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#### OVERACTION OF SUPERIOR OBLIQUE MUSCLE

*To the Editor*—North American authors frequently do not take notice of, or they overlook, the literature of other countries, especially of Latin America. This may be due to the impediment of language, and sometimes to the inferior place in which they place us in these countries. We also have been seriously criticized on a number of occasions when publications from this part of the continent have bibliographic deficiencies.

In these times, when *Panamericanismo* is not an empty word (as shown by the recent congress at Habana), we of the Western Hemisphere should aim to know one another better and should not consider each other strangers, since we all believe that "it's great to be an American."

I wish to note particularly that Latin-American publications were not mentioned in three recent articles by authors from the United States on subjects on which there was but little literature (Kirby, D B. Paralysis of Ocular Elevation With and Without Ptosis, *ARCH OPHTH* **35**:199 [March] 1946; Burian, H M. Sensorial Retinal Relationship in Concomitant Strabismus, *ibid* **37**:336 [March], 504 [April], 618 [May] 1947; Berke, R N. Tenotomy of the Superior Oblique Muscle for Hypertropia, *ibid* **38**:605 [Nov] 1947).

Berke states on page 608 "Hughes and Bogart (*Am J Ophth* **25**:911 [Aug] 1942) are the only authors who have advocated weakening an overacting superior oblique muscle in anomalies of the vertically-acting extraocular muscles." On page 609 he adds "Tenotomy or tenectomy of the superior oblique muscle has never been performed to relieve hypertropia in a patient with overaction of this muscle." The first assertion is wholly inaccurate, the second also is in error, for if the tenotomy or tenectomy of the superior oblique has not been performed, another operation instead has been successfully carried out. Meesman first (*Klin Monatsbl f Augenh* **105**:156 [Aug] 1940) and Malbran later (*Arch de oftal de Buenos Aires* **17**:337 [June] 1942) reported on the overaction of the superior oblique and its successful treatment by section of the trochlea. Both articles were published prior to the work of Hughes and Bogart, and neither was mentioned in Hughes's second publication (*Am J Ophth* **27**:1123, 1944).

JORGE MALBRAN, Buenos Aires, Argentina

Juncal 1330

#### SENSITIVITY TO APPLICATION OF SODIUM SULFACETIMIDE

*To the Editor*—The absence of allergic manifestations to sodium sulfacetimide when applied to the eye, either as a 30 per cent solution or

as a 10 per cent ointment, has led me to the frequent use of this drug in a large variety of external ocular conditions Dr Hedwig Kuhn (Sodium Sulfacetimide 30% Solution in Ophthalmology, *Tr Am Acad Ophth* **50:210** [May-June] 1946) stated that "to date, at least, the sodium sulfacetimide preparation [has never shown] an allergic reaction" She warned, however, that it is possible to have an allergic reaction Benedict and Henderson reported a case of sensitivity to sodium sulfacetimide (*Am J Ophth* **30:984** [Aug] 1947) I wish to add another case of sensitivity to this drug

Miss H G, a white woman aged 38, was referred to me for a lump on the right lower lid Examination showed a round, raised, soft, nodular mass, about 4 by 5 mm in diameter, with a small surrounding area of localized hyperemia She was told to use hot compresses and was given a prescription for an ointment containing sodium sulfacetimide in 10 per cent concentration On March 4 the cyst broke spontaneously and discharged through the skin just below the margin of the lid There was still a slight amount of tenderness She was told to continue with the application of sodium sulfacetimide and hot compresses She was seen on March 12, complaining that both the upper and the lower lid had become sore, itchy and painful Examination revealed a typical allergic dermatitis involving the upper and lower lids of the right eye She had been using the sodium sulfacetimide ointment faithfully, and she told me at this time that she was allergic to sulfonamide drugs in general She was instructed to discontinue use of the sulfacetimide ointment and to report back in three days She called me on March 15 and stated that the dermatitis had cleared up entirely

I wish to present this case as one of allergy to sodium sulfacetimide I believe that the drug should be used with caution in the case of a patient who gives a history of sensitivity to other sulfonamide compounds

KARL D MACMILLAN, M D, Pittsburgh

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# News and Notes

EDITED BY DR W L BENEDICT

## GENERAL NEWS

**The Revue internationale du trachome** — The organ of the Ligue contre le Trachome, founded in 1923 by Morax and Nicolle, and of the International Organization Against Trachoma, which has appeared in French and in English, will be republished shortly. The officers of the Ligue contre le Trachome are P. Bailliart, president, and Jean Sedán, secretary, 93, rue Sylvabelle, Marseille, and those of the International Organization Against Trachoma are A. F. MacCallan, president, and F. Wibaut, secretary, P. C. Hoofddraat 145, Amsterdam, Netherlands.

The contents of the first issue of the new series will contain a report of the meeting of the Ligue contre le Trachome (May 21, 1947) and an article by A. F. MacCallan on the ophthalmic campaign in Egypt. Dr. Jean Sedán will report on twenty-five years of action against trachoma and the question of hiring workers with trachoma. The following articles will also appear: "Treatment of Trachoma Overseas," P. Toulant, "Trachoma and the Union Française," Roger Nataf, "What Is Known About Trachoma?," E. Delanoe, "Cause of Trachoma," Roger Nataf, "Trachoma," Louis Rostkowski, "Denig's Operation for Trachoma," Noah Pines, "Inefficiency of Para-Aminobenzoic Acid in Treatment of Trachoma" and "Value of Evidence Against the Rickettsial Nature of the Disease," G. B. Bietti and G. Pasca.

Further information may be obtained from Dr. A. F. MacCallan, Westminster Hospital Medical School, 17, Horseferry Road, London.

**Alumni Meeting of Institute of Ophthalmology, Presbyterian Hospital, New York** — The alumni meeting of the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York was held on April 30 and May 1. The program consisted of the following papers: "A New Scleral Type of Implant—Motion Picture," Dr. Norman Cutler, "Retinoblastoma Autopsy Observations," Dr. George R. Merriam, "Determination of Lysozym in Tears," Dr. Ellen Regan, "The Fundus in Pheochromocytoma," Dr. John Cunningham, discussion by Dr. Gordon Bruce, "Preliminary Report on Use of Foreign Protein in Treatment of Intraocular Disease," Dr. Graham Clark, "Experimental Studies on Sympathetic Ophthalmia," Dr. Raymond Collins, "Experimental Results with a New Antibiotic," Dr. Murray Sanders, "Autoradiographic Studies on the Eye," Dr. Ludwig von Sallmann, "Clinical Experience with DFP [di-isopropyl fluorophosphate]," Dr. W. Conrad Stone, "Effect of Dicumaryl on the Visual Fields in Glaucoma," Dr. William P. McGuire, "Experimental Studies with Antibiotics and Antibiotic Mixtures in Treatment of Intraocular Infections," Dr. John Locke, "Orthoptics—Racket or Cure?" Dr. A. Lloyd Morgan, "Transplantation of Cornea in Keratoconus," Dr. Ramon Castroviejo, and "Investigation on Cases of Retrolental Fibroplasia," Dr. A. C. Unsworth. Demonstra-

tions were made of pupillography by Dr Otto Lowenstein, gonioscopy by Dr M U Tioncoso, physiologic optics by Dr Hardy, Dr Rand and Miss Rittler, artificial eyes by Mr E G Bethke, and radiotherapy of retinoblastoma by Dr George R Meiliam

*Rivista di oftalmologia* Continued as *Giornale italiano de oftalmologia*.—The Italian journal *Rivista di oftalmologia* is being continued as the *Giornale italiano de oftalmologia*, under the same editor (Prof B Alajmo and collaborators) and the management of the Clinica Oculistica Universitaria of Florence, Italy. The new journal will be issued every two months, its first number has appeared (1:1 [Jan-Feb], 1948)

**The Thigpen-Cater Eye Hospital**—The Thigpen-Cater Eye Hospital, in Birmingham, Ala., is organized on one floor of the Jefferson-Hillman Hospital, and provides for two ophthalmic operating rooms, eighteen beds for ophthalmic patients (ten additional charity beds), a full time photographer, a full time medical artist, orthoptic technician, residents' quarters, laboratory and executive offices for the department and for the Alabama Sight Conservation Association

**Annual Meeting of Wilmer Residents Association.**—The annual meeting of the Wilmer Residents Association was held at the Wilmer Ophthalmological Institute on April 14 to 16, 1948. The program consisted of the following papers: "Removal of the Eye," Dr Jack S Guyton, "A Two Piece Implant," Dr Charles E Iliff, "Treatment with Antibiotics and Chemotherapy of Experimental Ocular Tuberculosis," Dr Alan C Woods, "Retrolental Fibroplasia," Dr William C Owens and Dr Ella Uhler Owens, "Surgical Treatment of Coarctation of the Aorta and Pulmonic Stenosis," Dr Alfred Blalock, "Ocular Findings Before and After Operations for Congenital Heart Disease," Dr Richard A Hoffman, "Further Studies on Experimental Corneal Transplantation," Dr Alfred E Maumenee and Dr Walter Kornbleuth, "Experimental Use of Heparin in the Eye," Dr Malcolm W Bick, "Sterilization of Ophthalmic Solutions," Dr Samuel D McPherson Jr and Dr Donald Wood, "Nasopharyngeal Carcinoma," Dr Frank B Walsh, "Cerebral Representation of the Ocular Movements," Dr A Earl Walker, "Enzymatic Histochemistry and Its Application to Ophthalmic Research," Dr Jonas S Friedenwald, Dr Bernard Becker and Miss Jane Crowell, "Results of Cyclodiathermy for Glaucoma," Dr William G Marre, "Reabsorption of the Aqueous," Dr William F Hughes Jr, "Recurrent Erosion of the Cornea," Dr M Elliott Randolph, "Compression Tonometry," Dr Robert A Moses and Dr Mary G Biuno, "The Clinical Pathologic Conference," Dr Jonas S Friedenwald and Dr Robert Day, "Experimental Ocular Histoplasmosis," Dr Robert Day, "Surgical Treatment of Congenital Cataract," Dr Cecil Bagley, "Epivascular Choroidal Pigment Streaks Their Pathology and Medical Prognostic Significance," Dr Roy O Scholz, "Long Term Observation of Patients with Retrobulbar or Optic Neuritis," Dr Robert W Haines, "Review of Recent Work in Visual Physiology," Dr Samuel A Talbot, "Practical Principles in Treatment of Vascular Conditions of the Retina," Dr Angus L MacLean, "Harada's Disease," Dr Mary G Biuno and Dr Samuel D Mc

Pheison J1, "Synaptic Transmission with Reference to the Retina," Dr Stephen W Kuffler, "Bacterial Hypersensitivity and Its Relation to Ocular Disease," Dr Alan C Woods and Dr Ronald Wood

### SOCIETY NEWS

#### New Officers of Pan-American Association of Ophthalmology —

Dr Conrad Berens, of New York, was elected president of the Pan-American Association of Ophthalmology at the Third Pan-American Congress of Ophthalmology, held in Habana, Cuba, Jan 4 to 10, 1948. It was decided to hold the next congress in Mexico, D F, Mexico, early in 1952.

Twelve vice presidents were elected at the Habana meeting, the representation being based on the number of ophthalmologists in each of the member countries. Those elected were as follows: Argentina, Dr Esteban Adroque, Buenos Aires; Bolivia, Dr Aniceto Solares, Sucre; Brazil, Dr Ivo Correa Meyer, Porto Alegre; Canada, Dr John MacMillan, Montreal; Chile, Dr Santiago Barrenechea, Santiago; Columbia, Dr Francisco Varnaza, Bogotá; Costa Rica, Dr Alexis Aguero, San Jose; Cuba, Dr Miguel Branly, Habana; Ecuador, Dr J M Varas Samaniego, Guayaquil; Guatemala, Dr Jose Miguel Medrano, Guatemala City; United States, Dr Frederick C Cordes, San Francisco, and Dr William L Benedict, Rochester, Minn. Dr Moacyr E Alvaro, Sao Paulo, Brazil, was reelected secretary for the countries south of Panama, and Dr Thomas D Allen, Chicago, was elected to succeed Dr Berens for the corresponding position for the countries north of Panama. The following were appointed assistant secretaries: Dr Brittain F Payne, New York; Dr Jorge Balba, Buenos Aires; Dr Manoel A da Silva, Sao Paulo, and Dr F Palomino Dena, Mexico, D F, Mexico.

The congress adopted "statutes and by-laws," establishing the Pan-American Association of Ophthalmology as a continuing organization, with the objectives of fostering the progress of ophthalmology, establishing contacts among ophthalmologists of the Western Hemisphere and promoting measures to conserve eyesight and prevent blindness among the peoples of the hemisphere. To achieve these aims, permanent committees were established to deal with the following matters, among others: encouragement of research, glaucoma, trachoma, lighting and optics, contact lens center, orthoptics, prevention of blindness, neuro-ophthalmology, legal and industrial ophthalmology, standardization of ophthalmic hospitals and clinics, inter-American medical relationships, establishment and guidance of ophthalmologic societies and scientific cinematography.

The statutes provide for an Inter-American Federation of Ophthalmologic Societies and for a Bureau of Professors of Ophthalmology, who are to encourage the formation of centers for graduate study and stimulate the teaching of ophthalmology throughout the hemisphere, to effect interchanges of professors and alumni among teaching centers, to arrange for and manage prizes and scholarships and to arrange for examinations of, and issue certificates of proficiency to, physicians who seek them. In the last-mentioned function, the bureau's activities are not intended to interfere with independent examining boards already functioning efficiently.

A board of censors was formed to supervise the relations of Association members to the lay press. According to the resolution adopted at

Habana, local representatives of the Association's press relations committee must approve publication of articles in the lay press concerning any member

**New York Society for Clinical Ophthalmology.**—The New York Society for Clinical Ophthalmology recently elected the following officers for the year 1948-1949: president, Dr Benjamin Esterman, vice president, Dr Sidney A. Fox, recording secretary, Dr Bernard Kronenberg, corresponding secretary, Dr Leon H. Ehrlich, treasurer, Dr Edward Saskin, historian, Dr Howard J. Agatston, committee chairman, Dr Adolph Posner (program), Dr Frederick H. Theodore (instruction hour), Dr Max Chamlin (legislative), Dr Bernard Fread (membership), Dr David A. Newman (industrial). Dr Daniel Kravitz, the retiring president, was elected to the advisory council.

**Ophthalmological Journal Club.**—A meeting was held at the home of Dr Samuel V. Abraham, 610 North Linden Drive, Beverly Hills, Calif., April 15, 1948, for the purpose of organizing the Ophthalmological Journal Club.

The primary interest of the club is to abstract current literature on ophthalmology and related subjects for the purpose of presenting it to the members for discussion.

The meetings will be held the first Thursday of each month at 8 p. m., at 416 Bedford Drive, Beverly Hills, Calif.

Dr Samuel V. Abraham will be chairman of the club.

## Book Reviews

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**Clinical Neuro-Ophthalmology** By Frank B. Walsh, M.D., F.R.C.S. (Edin.) Price, \$18 Pp 1,532, with 384 illustrations Baltimore The Williams & Wilkins Company, 1947

In recent years great advances have been made in neuro-ophthalmology, and knowledge of the intricate central connections of the ocular apparatus has been much advanced. An up-to-date treatise is therefore most timely, and this has been accomplished by Dr. Walsh with this monumental work of 1,532 pages, which is an exhaustive and systematic exposition of neuro-ophthalmology, with particular emphasis on the clinical side.

One of the great difficulties in a work of this kind is a proper classification. Dr. Walsh has been much influenced by the outline used by Dr. F. R. Ford in his "Diseases of the Nervous System in Children" and has chosen a classification which is based on etiology, with due emphasis on clinical features.

In the first chapter, on the "Visual Pathways and the Diagnosis of Lesions Situated at Different Levels," the subject is divided into the following parts: (1) anatomy, (2) arrangement of visual fibers in the optic pathway, (3) topical diagnosis of the visual pathways, with particular reference to the visual fields, (4) topical diagnosis of lesions in the higher visual pathways, aphasia, apraxia, agnosia, alexia.

The second chapter describes the other cranial nerves and the topical diagnosis of their lesions. This is followed by chapters on the following subjects: the autonomic system, the pupil normal and abnormal accommodation, the eyelids and extraocular muscles, papilledema, optic neuritis, optic atrophy, congenital and developmental abnormalities and diseases of the eyes and central nervous system, infections and parasitic invasions of the nervous system and their ocular signs, including an outline of the nervous system and ocular syphilis, hereditary and degenerative disease, toxic and metabolic diseases, disorders of muscles, vascular lesions and circulatory disorders of the nervous system, ocular signs, ocular and intracranial tumors and related conditions, injuries by physical agents, ocular signs, epilepsy, migraine and other paroxysmal disorders, ocular signs of hysteria, malingering and traumatic neurosis, the psychiatric aspects of ocular disorders (Dr. M. Levin), drugs, poisons and toxic amblyopias.

These titles indicate the thorough manner in which the subject has been treated, and the reader is soon impressed with the completeness of the work and the vast amount of information it contains. In a subject as difficult as neurologic diagnosis a detailed description of the basic sciences is desirable, and this has been included in the text of each chapter. Many case reports are added to illustrate the variability and the problems of differential diagnosis. At the end of each chapter there is a list of references which, without claiming to be complete, is designed to facilitate further study. There are 384 illustrations. An index of 108 pages completes the volume and brings also a list of the case histories.

To Dr Walsh are due our hearty congratulations on the completion of this colossal task, the importance of which is signified by the manifold interest of its contents, as well as by the author's deep study and long experience, at both the Johns Hopkins and the Baltimore City Hospital

The book presents a complete outline of the subject and will serve as a valuable reference book. The illustrations and print are admirable, but the book is rather heavy to handle and its length is somewhat formidable

ARNOLD KNAPP

**Transactions of the Ophthalmological Society of Australia (British Medical Association).**—Volume 6 Price, 15 S Pp 155 Sydney, Australia Australasian Medical Publishing Company, Ltd, 1946

These *Transactions* record the proceedings of the Australian Ophthalmological Society at its sixth annual meeting held on Oct 23, 1946, in Melbourne. The president was J R Anderson, whose presidential address, "Our Common Enemy, Blindness," occupies more than 25 per cent of the volume. Following this are two papers by the guest of honor, Air Commodore P C Livingston, of the Royal Air Force. In the first of these, "Experiences in Night Vision in the Royal Air Forces," he recounts the development of testing methods in use in the R A F. He discriminates between the perception of light minimum (an elementary difference in threshold discrimination) and variations in the power to synthesize form. The latter was obviously the more important, and so the well known rotating hexagon was devised. It is fully described and illustrated in the paper. It was further found that the scotopic field varied considerably from the field obtained at photopic levels. All scotopic fields demonstrated a round or oval central absolute scotoma, and it was often possible to plot the roots and main branches of the retinal vessels. In the second paper, "Heterophoria in Aircrew: Its Clinical and Psychological Significance," Livingston describes the development and technic of investigative procedures and the significance of the findings. He expresses the belief that many persons with heterophoria fly successfully, and also that many fail but succeed later when the heterophoria is corrected. He is convinced that there are two basic types of heterophoria: first, the type for which the child learns to compensate by experience and, second, the variety which follows illness or fatigue.

The subject of orthoptic treatment is continued by Diana S Mann out of a considerable experience with private, public and Air Force patients. She states her belief that orthoptic treatment has never straightened a constantly convergent pair of eyes. She has never been able to obtain stereoscopic vision when a squint had become constant under the age of 1 year. If binocular vision has never existed, it can never be developed. She has obtained her best results in dealing with eyestrain that did not respond to correction of refractive error, and, to a lesser extent, she is encouraged by her results in convergence deficiency.

Nutritional diseases in prisoners of war are discussed in papers by S Gerstman ("A Survey of Retrobulbar Neuritis in Prisoners of War"), by C Colvin ("Ocular Disturbances Associated with Malnutrition") and by R Maynard ("Blindness Among Prisoners of War"). Gerstman is skeptical of temporal pallor and recommends use of the 2 and 4 meter screens for mapping central scotomas. He thinks that the prognosis in such cases is not encouraging. Colvin points out that ocular symptoms in

malnutrition are slow in appearing and states that of persons in the same area and receiving the same diet, some will exhibit ocular symptoms and others will not. Maynard reports on the pathologic sections of two globes enucleated from patients with gross malnutrition. The sections illustrated a diffuse demyelinating lesion of the optic nerve, combined with degeneration of the ganglion cells and nerve fibers of the internal layers of the retina.

In a short article, entitled "The Future of Australian Ophthalmology," K. O'Day points out that most Australian ophthalmologists had been trained in England and indicates the advisability of establishing faculties for such training at home.

J. Maude reports a case of "angioid streaks of the retina and pseudo-xanthoma elasticum." This disease must be much rarer in Australia than it is in the United States, where numerous examples of the syndrome have been reported. It is unfortunate that Maude's bibliography does not include the paper by Gronblad, who first detected the relation of the two diseases.

In his paper, entitled "Inherited Retinal Detachment," J. B. Hamilton has compiled a pedigree of sufferers from this disease. He examined 10 patients and found that pseudoglioma and retinal cysts were peculiar features, aniridia was a complication, hypermetropia was the invariable rule and no history of trauma was ever elicited. He is convinced that congenital cystic disease of the retina in its infantile form may be, like congenital cystic disease of the lung, part of a generalized cystic process throughout the body.

The interest in the effect of maternal rubella on the infantile eye continues to be high in the country where the work originated. E. O. Marks ("Pigmentary Abnormality in Children Congenitally Deaf Following Maternal German Measles") examined the children in a school for the blind and deaf. Nearly half the deaf children born in the epidemic years showed marked pigmentary abnormalities resembling atypical retinitis pigmentosa. Those born in other years had normal fundi. Of 38 deaf children with a history of maternal rubella, 17 had abnormally pigmented fundi. Of 37 deaf children with abnormally pigmented fundi, 21 had a history of maternal rubella.

"Intracapsular Cataract Extraction. Its Most Serious Complication" is the title of a paper by F. Roberts. The complication is a progressive contraction upward of the pillars of the iris due to the formation of a fibrous tissue band in the ciliary body above.

Continuing his work on glaucoma due to trauma, A. D'Ombrian ("Concussion Glaucoma") has reached a conclusion as to the etiologic mechanism of the condition. He states the belief that sufficient trauma may cause fibrosis of the ciliary region or the venous capillary bed.

In the final paper the "Choice of Operation in Glaucoma," by N. Macindoe, the author counsels repeated paracentesis in cases of corneal ulcer, lime burns and severe hyphema complicating secondary glaucoma. With dislocation of the lens, he prefers a posterior sclerotomy before the lens is removed, and in cases of iris bombé he advises iridectomy. In cases of acute primary glaucoma, he suggests a posterior sclerotomy, followed by a filtering operation. In dealing with chronic glaucoma, he prefers iridencleisis in cases in which a subsequent cataract operation is planned and in which the patient is old and has advanced glaucoma. If the eye is quiet, he performs trephination, if it is not, he does a Lagrange operation.

G. M. BRUCE

## CHOICE OF SULFONAMIDE DRUGS FOR LOCAL USE

IRVING H. LEOPOLD, M.D., D.Sc.

AND

WILLARD H. STEELE, M.D.  
PHILADELPHIA

THE increasing availability of penicillin, and more recently of streptomycin, has led to the less frequent use of the sulfonamide compounds as ocular therapeutic agents. In several instances these antibiotics are superior to the sulfonamide compounds. Penicillin is locally effective in the presence of purulent material. It is very effective against ocular infections due to many gram-positive organisms, and streptomycin is effective against several gram-negative organismal infections.

There are many occasions, however, when the so-called antibiotics will not be helpful. Organisms become resistant to the effects of penicillin, and especially to streptomycin. These agents rapidly lose their potency when not kept under refrigeration, particularly when in solution. Some patients acquire hypersensitivity to penicillin or streptomycin. In any of these predicaments the substitution of one of the sulfonamide drugs might be beneficial.

Although it is not universally accepted,<sup>1</sup> there is evidence that the sulfonamide compounds are effective as bacteriostatic agents when applied locally to the ocular tissues.<sup>2</sup> It has been found that the higher the concentration of the sulfonamide drug obtained in the infected tissue, up to a point, the better have been the results in controlled ex-

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The material presented in this paper is derived in part from work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania.

1 Lyons, C. Chemotherapy in Management of Wounds, *JAMA* **113**:215 (Jan 25) 1947. Cole, W. T. S., Hamilton-Paterson, J. L., and Sorsby, A. The Suitability of Experimental Corneal Lesions for Evaluating Local Sulphonamide Therapy, *Brit J Ophth* **29**:150 (March) 1945.

2 (a) Rambo, V. C. Treatment of Pathological Ocular Conditions with Sulfanilamide, *Am J Ophth* **21**:739 (July) 1938. (b) Johnstone, I. L. Sulphonamide Treatment of Hypopyon Ulcer of the Cornea, *Brit M J* **1**:887 (June 14) 1941. (c) Robson, J. M., and Scott, G. I. Effect of Certain Chemotherapeutic Agents on Experimental Eye Lesions Produced by *Staphylococcus Aureus*, *Nature, London* **149**:581 (May 23) 1942. (d) Local Effectiveness of Sodium Sulphacetamide in Treatment of Experimental Ulcers of the Cornea, *Brit M J* **1**:5 (Jan 3) 1942. (e) Local Treatment of

(Footnote continued on following page)



perimental infection<sup>3</sup> Comparisons of the various methods of administration, as well as of the various sulfonamide drugs, have been made in an effort to determine the simplest method of reaching the highest concentration in a particular tissue<sup>4</sup> The problem of the choice of a particular sulfonamide drug has been complicated with many factors Each year new sulfonamide compounds have become available Each compound has had a particular merit extolled Most of these substances have been tried in the treatment of pneumonia, gastrointestinal infections and in urinary infections The usefulness of only a few has been tested in the management of ocular infections and their ability to penetrate ocular tissues measured In an effort to review the many problems encountered in the selection of the proper sulfonamide compound and the acceptable local methods of administration, the following experiments are reported

#### METHOD OF STUDY

Normal rabbit eyes were used The rabbits were chinchillas, weighing approximately 4 Kg The aqueous humor of these eyes yielded from 0.2 to 0.25 cc per punc-

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Experimental Pyocyanus Ulcers of the Cornea with Albucid Soluble, *Nature*, London **148** 167 (Aug 9) 1941 (*f*) Scott, G I, and others Discussion of the Value of Sulfonamides in Ophthalmology, *Tr Ophth Soc U Kingdom* **62** 3, 1942 (*g*) Dickson, R M Traumatic Ulcer of Cornea with Special Reference to Coal Miners, *Brit J Ophth* **26** 529 (Dec) 1942 (*h*) Bellows, J G Chemotherapy in Ophthalmology, *Tr Am Acad Ophth* **47** 19 (Sept) 1942 (*i*) Leopold, I H, and Scheie, H G Studies with Microcrystalline Sulfathiazole, *Arch Ophth* **29** 811 (May) 1943 (*j*) Thygeson, P Sulfonamide Compounds in Treatment of Ocular Infections, *ibid* **29** 1000 (June) 1943 (*k*) Thygeson, P, and Braley, A E Local Therapy of Catarrhal Conjunctivitis with Sulfonamide Compounds, *ibid* **29** 760 (May) 1943 (*l*) von Sallmann, L Sulfadiazine Iontophoresis in Experimental Pyocyanus Ulcer of Rabbit Cornea, *Am J Ophth* **25** 1292 (Nov) 1942 (*m*) Alvaro, M E Clinical Effects of Local Use of Sulfonamides on Eyes, *ibid* **28** 497 (May) 1945 (*n*) Vorisek, E A Evaluation of the Newer Therapeutic Agents in Ophthalmology, *ibid* **30** 29 (Jan) 1947

3 Robson and Scott (footnote 2*c*, *d* and *e*) Scott and others<sup>2*f*</sup> von Sallmann<sup>2*i*</sup>

4 Leopold and Scheie<sup>2*i*</sup> von Sallmann<sup>2*i*</sup> Guyton, J Use of Sulfonamide Compounds in Ophthalmology, *Am J Ophth* **22** 833 (Aug) 1939, Local Use of Sulfonamide Compounds in the Eye, *ibid* **24** 292 (March) 1941 Mengel, W G Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, *Arch Ophth* **22** 406 (Sept) 1939 Chinn, H, and Bellows, J G Corneal Penetration of Sulfanilamide and Some of Its Derivatives, *ibid* **27** 34 (Jan) 1942 Pan, S Y Distribution of Sulfanilamide in the Ocular Fluids and Tissues After Local Application, *Proc Soc Exper Biol & Med* **46** 31 (Jan) 1941 Gallardo, E, and Thompson, R Sulfonamide Content of Aqueous Humor Following Conjunctival Application of Drug Powders, *Am J Ophth* **25** 1210 (Oct) 1942 Boyd, J Sodium Sulfathiazole Iontophoresis, *Arch Ophth* **28** 205 (Aug) 1942 Robson, J M, and Tebrich, W Penetration of a Water-Soluble Sulfonamide, Sodium Sulphacetamide into the Eyes of Rabbits, *Nature*, London **148** 695 (Dec 6) 1941

ture At the desired interval after application of the sulfonamide preparation, the eyes were thoroughly washed with a 1.4 per cent solution of sodium chloride, and 2 drops of 1 per cent tetracaine hydrochloride was instilled for local anesthesia. Punctures were made into the anterior chamber with a tuberculin syringe and a no. 22 hypodermic needle. The method of Bratton and Marshall<sup>5</sup> was used for determining the levels of free sulfonamide. Standard curves for known quantities of each sulfonamide compound were determined. Recoveries on normal aqueous humor showed that an error of less than 3 per cent could be expected with this method. An Evelyn photoelectric colorimeter was used in the procedure.

Sulfonamide compounds in their acid form are not sufficiently soluble in water to be used as solutions in clinical work. Their sodium salts are freely soluble, and therefore solutions of 5, 10 and 20 per cent concentrations were employed in these experiments. Calcium sulfadiazine is soluble up to 5 per cent, and only this concentration was used. Ammonium sulfadiazine was tried in 10 per cent concentration.

### RESULTS

Table 1 records the concentration of the sulfonamide compound in the aqueous humor fifteen minutes after application to normal rabbit

TABLE 1—*Penetration into the Anterior Chamber of Normal Rabbit Eyes of Locally Applied 10 Per Cent Solutions of Sodium Salts of Various Sulfonamide Compounds and 5 Per Cent Calcium Sulfadiazine*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor						
10% Sodium Sulfadiazine	10% Microcrystalline Sulfadiazine	10% Sodium Sulfacetimide	10% Sodium Sulfamezathine	10% Sodium Sulfamerazine	10% Ammonium Sulfadiazine	5% Calcium Sulfadiazine
0.06	0.11	0.17	1.71	1.6	0.68	0.57
0.23	0.17	0.28	0.68	0.46	0.91	0.34
0.23	0.06	0.23	2.5	0.57	1.30	0.40
0.26	0.57	0.17	1.8	0.23	0.91	0.45
0.28	0.50	0.24	1.6	0.23		0.50
0.34	0.23	0.26				
0.23						
0.34						

eyes of 4 drops of 10 per cent solutions of sodium sulfadiazine, 10 per cent ammonium sulfadiazine, 5 per cent calcium sulfadiazine, 10 per cent sodium sulfacetimide (sodium salt of para-aminobenzene sulfonyl-acetylimide, acetylsulfanilamide), 10 per cent sodium sulfamezathine (sodium salt of the dimethyl derivative of sulfadiazine) and 10 per cent sulfamerazine sodium U.S.P. The levels after applying 0.3 Gm. of 15 per cent microcrystalline sulfadiazine are also recorded. Only sodium sulfamezathine penetrated significantly better than the others.

Table 2 presents the results when these agents were applied in an ointment base (samples of aqueous humor were withdrawn fifteen minutes after application of the ointment). No significant difference could be detected between the various compounds, nor did it matter whether the ointment base was of the oil in water type, such as Fried-

<sup>5</sup> Bratton, A. C., and Marshall, E. K., Jr. New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537, 1939.

enwald-Fuqua ointment,<sup>6</sup> or the water in oil type, such as "aquaphor"<sup>7</sup> The aqueous levels obtained with ointment preparations in the normal eye were approximately the same as those with solutions The acid form also penetrated as well as the sodium salt

TABLE 2—*Penetration into the Anterior Chamber of Sulfonamide Compound in Ointment Bases*

Milligrams of Sulfonamide Compound per 100 Cc of Aqueous Humor				
10% Sulfadiazine	10% Sodium Sulfadiazine	10% Microcrystalline Sulfadiazine "AQUAPHOR" BASE	10% Sodium Sulfacetimide	10% Sulfacetimide
0.57	0.00	0.23	0.34	0.23
0.00	0.23	0.34	0.68	0.66
0.00	0.00	0.46	0.23	0.23
0.06	0.11	0.44	0.80	0.46
0.00	0.06		0.34	0.34
FRIEDENWALD-FUQUA BASE				
0.11	0.11	0.23	0.06	0.11
0.23	0.46	0.06	0.46	0.11
0.11	0.46	0.06	0.06	0.23
0.17	0.34	0.17	0.24	0.22

In table 3 are given the results of repeated application of the drops, 4 drops every fifteen minutes for three doses, and withdrawal of the aqueous humor fifteen minutes after instillation of the last drop The concentrations in the aqueous humor were raised slightly over those with one application of 4 drops, but not to an adequate therapeutic level in any eye

TABLE 3—*Penetration into Anterior Chamber of 10 Per Cent Solutions of Sodium Sulfacetimide and Sodium Sulfadiazine Repeatedly Applied\**

Milligrams of Sulfonamide Compound per 100 Cc of Aqueous Humor	
10% Sodium Sulfadiazine	10% Sodium Sulfacetimide
0.10	0.28
0.57	0.34
0.23	0.10
0.90	0.80
0.88	0.90

\*Four drops of the solution was applied every fifteen minutes for three doses fifteen minutes after the last application (one hour after the first application) the specimens of aqueous were taken

Table 4 records the levels in the aqueous after application of 20 per cent solutions of sodium sulfadiazine and sodium sulfacetimide Four drops was applied, and punctures were made fifteen minutes later No significant increase was noted in the normal eye over the concentration reached after the use of 10 per cent solutions These results indicated that an adequate level in the aqueous humor cannot be expected from application of solutions in the normal rabbit eye

6 The Friedenwald-Fuqua ointment base contains benzyl benzoate, 5 per cent, peanut oil, 37 per cent, anhydrous wool fat, 8 per cent, cetyl alcohol, 10 per cent, glycerin monostearate, 10 per cent, and white petrolatum USP, 25 per cent

7 "Aquaphor" is an ointment base containing 6 per cent of a group of esters of cholesterol (chiefly oxysterol) in an aliphatic hydrocarbon (petrolatum) base

Drops of sodium sulfadiazine and sodium sulfacetimide, 10 per cent each in a 0.1 per cent solution of "duponol" (fatty alcohol sulfates) were applied to the right eyes of a series of normal rabbits, and the same sulfonamide drugs were applied in equal quantity to the control (left) eyes without a wetting agent. The results are recorded in table 5. The same procedure was repeated with these compounds in an ointment base. It is shown in this table that the use of a detergent definitely increases the penetration into the anterior chamber of the sulfonamide compound in ointment or in liquid form. The corneas do

TABLE 4—*Penetration into the Anterior Chamber of Normal Rabbit Eyes of Locally Applied 20 Per Cent Sodium Sulfadiazine, 20 Per Cent Sodium Sulfacetimide and 20 Per Cent Microcrystalline Sulfadiazine\**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor		
20% Sodium Sulfadiazine	20% Microcrystalline Sulfadiazine	20% Sodium Sulfacetimide
0.20	0.65	0.11
0.11	0.17	0.28
0.45	0.29	0.46
0.34	0.11	0.23
0.33	0.17	0.57
	0.30	

\*Applications in each instance were 4 drops, or 0.3, and specimens were taken by puncture fifteen minutes after the last application.

TABLE 5—*Influence of Detergent on Penetration of Sulfonamide Preparation into Anterior Chamber of Normal Rabbit Eye\**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor			
10% Sulfadiazine in Friedenwald-Fuqua Ointment*	10% Sulfadiazine and "Duponol," 0.1% in Ointment	10% Solution of Sodium Sulfadiazine	10% Solution of Sodium Sulfadiazine and "Duponol," 0.1%
0.0	0.0	0.0	0.0
0.11	0.44	0.28	1.25
0.23	0.68	0.34	0.91
0.17	1.37	0.23	0.66
10% Sulfacetimide in Friedenwald-Fuqua Ointment	10% Sulfacetimide in Ointment and "Duponol," 0.1%	10% Solution of Sodium Sulfacetimide	10% Solution of Sodium Sulfacetimide and "Duponol," 0.1%
0.0	0.0	0.0	0.0
0.11	2.96	0.11	2.62
0.17	0.67	0.17	0.83
0.23	2.01	0.26	0.86

\*Four drops was applied and specimens were taken fifteen minutes after the last drop.

not stain after such treatment. The concentrations obtained in the aqueous are still not theoretically adequate, but indicate that the corneal levels are at, or are approaching, the therapeutic level. These results simply confirm those of Bellows and others,<sup>8</sup> who have demonstrated the increased penetration of locally applied sulfonamide compounds with various detergents.

All these studies were repeated using rabbit eyes which were contaminated with a measured quantity (0.4 mg.) of mustard gas (2-chloroethyl sulfide). Such a lesion produces loss of corneal epithelium and a severe, persistent inflammatory reaction of the anterior segment.

<sup>8</sup> Leopold and Scheie.<sup>21</sup> Bellows, J., and Gutman, M. Application of Wetting Agents in Ophthalmology, Arch. Ophth. 30:352 (Sept.) 1943. Ginsburg, M., and Robson, J. M. Effect of Detergent on the Penetration of Sodium Sulphacetamide into Ocular Tissues, Brit. J. Ophth. 29:185 (April) 1945.

It is evident from the analyses presented in tables 6, 7 and 8 that the penetration of each of the sulfonamide drugs is greatly increased in the eyes previously burned with mustard gas. It is also evident that one may expect high penetration values even nine days after the initial burn. Sodium sulfacetimide gives higher aqueous levels than sodium sulfadiazine. The sodium salts of sulfamerazine and sulfamezathine penetrate the burned eye better than sodium sulfadiazine, but not quite as well as sodium sulfacetimide.

From the results shown in tables 9 and 10, it is evident that the acid salt of the sulfonamide compounds, as well as their sodium salts,

TABLE 6—*Penetration of 10 Per Cent Solution of Sodium Sulfadiazine\**

Normal Eyes	Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor Eyes Burned with Mustard Gas			
	24 Hours Previously	48 Hours Previously	96 Hours Previously	9 Days Previously
0 00	31 1	53 8	61 6	40 0
0 20	33 5	46 1	46 4	42 0
0 30	34 2	46 1	46 4	42 0
0 23		81 4	55 0	59 2
0 26		48 3		
0 33		60 7		
0 20		79 3		

\*Four drops was applied and specimens were taken fifteen minutes after the last drop

TABLE 7—*Penetration of 10 Per Cent Solution of Sodium Sulfacetimide\**

Normal Eyes	Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor Eyes Burned with Mustard Gas			
	24 Hours Previously	48 Hours Previously	96 Hours Previously	9 Days Previously
0 17	124 8	87 2	100 8	83 2
0 28	72 8	119 2	75 2	74 0
0 24	84 0	103 6	52 0	32 4
0 21		52 0		
0 21		80 0		
0 18		88 0		

\*Four drops was applied and specimens were taken fifteen minutes after the last drop

TABLE 8—*Penetration of 10 Per Cent Sodium Sulfamezathine and 10 Per Cent Sodium Sulfamerazine in Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Drug per 100 Cc. of Aqueous Humor	
Sodium Sulfamezathine, 10%	Sodium Sulfamerazine, 10%
O D	O S
37 6	54 3
37 6	44 5
34 2	58 4
38 4	55 0
40 0	57 5

penetrate much more readily in eyes which have been burned with mustard gas. However, the penetration of the acid salt of each sulfonamide compound was not so great as the sodium salt. Also, the penetration of the sodium salt was much greater in a fifteen minute period from a solution vehicle than it was from an ointment vehicle. It is also evident from table 10 that the type of ointment base was an important factor in penetration of the drug into mustard-burned eyes. Here it may be seen that both sodium sulfadiazine and sodium sulfacetimide penetrated much more rapidly from an ointment base such as the

Friedenwald-Fuqua type, which is similar to an oil in water base, than they did from an ointment base such as "aquaphor," which is a water in oil base

From the results in table 11, it is evident that the sulfonamide drugs in an ointment base reached a high level in the aqueous after

TABLE 9—*Penetration of 10 Per Cent Sulfadiazine and 10 Per Cent Sulfacetimide in "Aquaphor" Ointment*

Milligrams of Sulfonamide Drug per 100 Cc. of Aqueous Humor			
10% Sulfadiazine in "Aquaphor" Ointment		10% Sulfacetimide in "Aquaphor" Ointment	
Eyes Burned with Mustard Gas 24 Hr Previously		Eyes Burned with Mustard Gas 24 Hr Previously	
Normal Eyes		Normal Eyes	
0 06	0 67	0 44	0 80
0 11	0 93	0 33	0 91
0 20	1 46	0 60	1 14

TABLE 10—*Penetration of 10 Per Cent Sodium Sulfadiazine and 10 Per Cent Sodium Sulfacetimide in Various Ointment Bases*

Milligrams of Sulfonamide per 100 Cc. of Aqueous Humor							
10% Sodium Sulfadiazine Ointments				10% Sodium Sulfacetimide Ointments			
Eyes Burned with Mustard Gas				Eyes Burned with Mustard Gas			
Normal Eyes	24 Hr	48 Hr	72 Hr	Normal Eyes	24 Hr	48 Hr	72 Hr
Previously	Previously	Previously	Previously	Previously	Previously	Previously	Previously
*F F	"Aquaphor"	F F	F F	F F	"Aquaphor"	F F	F F
0 34	0 80	14 4	12 8	0 68	10 83	73 6	50 6
0 38	0 63	11 2	13 6	0 46	12 77	43 2	61 6
0 17	1 06	19 2	14 4	0 36	6 84	89 6	79 1
							92 0
	FF				FF		
	9 9				48 0		
	18 7				40 8		
	16 6				53 0		
	Hydrous Wool Fat—Petrolatum Base						
	0 92						
	1 2						
	1 4						
	1 2						
	Vanisol†						
	6 8						
	6 8						
	7 1						
	5 9						

\*Friedenwald-Fuqua ointment base

†"Vanisol" consists of sodium stearate, 20 per cent, cetyl alcohol, 5 per cent, glycerin mono-stearate, 8 per cent, and water, 67 per cent.

TABLE 11—*Penetration of Sulfonamide Compounds in Friedenwald-Fuqua Ointment Base in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously\**

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor			
Ointment in Contact with Cornea			
Sodium Sulfadiazine			
15 Min	1 Hr	6 Hr	24 Hr
14 4	24 0	2 05	1 20
11 2	20 0	2 17	0 40
19 2	20 0	1 94	0 51
Sodium Sulfacetimide			
73 6	144 0	0 46	0 13
43 2	137 6	0 23	0 67
89 6	104 0	1 10	0 23

\*Values are expressed as milligrams of the sulfonamide compound per hundred cubic centimeter of aqueous humor

being in contact with mustard-burned eyes for one hour, that the drugs passed from the aqueous humor at such a rate that adequate levels were not present after six hours and that only very small quanti-

ties remained at the end of twenty-four hours. It is apparent that sulfadiazine tended to pass out of the anterior chamber less rapidly than sulfacetimide. These findings indicate that an ointment would have to be applied a minimum of four times a day, and preferably oftener, in order to maintain a theoretically adequate concentration in the aqueous humor in such eyes. For similar reasons (table 12), solutions should be applied every two hours.

TABLE 12—*Persistence of Sodium Sulfadiazine in Aqueous Humor of Mustard-Burned Rabbit Eyes After Application of Four Drops of 10 Per Cent Solution of Sodium Sulfadiazine*

Milligrams of Sulfadiazine per 100 Cc. of Aqueous Humor Interval After Application of Last Drop			
15 Min	1 Hr	2 Hr	4 Hr
30.1	3.7	1.14	0.80
32.0	3.0	2.05	0.68
30.4	4.2	2.14	0.48
32.8	4.9	1.90	0.36

In table 13 is recorded the penetration of microcrystalline sulfadiazine in ointment into the anterior chamber of eyes burned with mustard gas twenty-four hours previously. It is evident that the levels obtained are not better than the levels demonstrated for the macrocrystals of sulfadiazine in the same ointment (compare with table 9). It is apparent that the addition of "duponol M E dry," 0.1 per cent, increased the penetration of the microcrystalline sulfadiazine in eyes burned with mustard gas. However, the values obtained were still not so great as those obtained with the sodium salt.

TABLE 13—*Influence of Detergent on Penetration of Microcrystals of Sulfadiazine in "Aquaphor" in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc. of Aqueous Humor	
10% Microcrystalline Sulfadiazine in "Aquaphor"	10% Microcrystalline Sulfadiazine in "Aquaphor" and 0.1% "Duponol"
O.D.	O.S.
0.80	3.30
1.50	1.90
0.80	1.80

Specimens of aqueous were withdrawn fifteen minutes after application of the ointment.

It is evident from the data in table 14 that the addition of "duponol" in 0.1 per cent concentration increased the penetration of sodium sulfadiazine in ointment into eyes burned with mustard gas. The addition of the detergent placed the penetration values of sodium sulfadiazine in the realm of the values obtained with sodium sulfacetimide.

The results indicated in tables 2, 10 and 15 again show that, although the ointment base made no significant difference in the penetration of the sulfonamide compound into normal eyes, it did make an important difference in eyes with damaged epithelium. "Aquaphor" does not allow as high aqueous levels to be reached as does the Frieden-

wald-Fuqua type of ointment. It is evident from a comparison of table 15 with table 10 that, although a 5 per cent solution of sodium sulfacetimide gives adequate aqueous concentrations, they are much lower than the levels obtained with the 10 per cent sodium sulfacetimide preparation in the same ointment base.

TABLE 14—*Influence of Detergent on Penetration of 10 Per Cent Sodium Sulfadiazine in Friedenwald-Fuqua Ointment Base into Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfadiazine per 100 Cc	
10% Sodium Sulfadiazine in Friedenwald-Fuqua Ointment	10% Sodium Sulfadiazine in Friedenwald-Fuqua Ointment plus 0.1% "Duponol"
O D	O S
10.0	34.3
17.5	46.9
19.6	45.0
22.0	40.0
16.0	42.7

TABLE 15—*Penetration of 5 Per Cent Concentrations of Sodium Sulfacetimide, Calcium Sulfadiazine and Sodium Sulfadiazine in Friedenwald-Fuqua, "Aquaphor" and "Vanisol" Ointment Bases into the Anterior Chamber of Rabbit Eyes Previously Burned with Mustard Gas*

Milligrams of Sulfonamide Compound per 100 Cc of Aqueous Humor				
5% Sodium Sulfadiazine in "Vanisol"	5% Calcium Sulfadiazine in "Vanisol"	5% Sodium Sulfacetimide in "Vanisol"	5% Sodium Sulfacetimide in Friedenwald-Fuqua Ointment	5% Sodium Sulfacetimide in "Aquaphor"
2.0	1.9	8.0	6.84	0.680
4.1	2.0	9.4	23.50	0.912
2.9	2.0	6.2	9.30	0.912

TABLE 16—*Concentrations in Aqueous Humor Fifteen Minutes After Instillation of Four Drops of 5 Per Cent Solutions of Calcium Sulfadiazine, Sodium Sulfadiazine and Sodium Sulfacetimide into Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc of Aqueous Humor		
5% Calcium Sulfadiazine	5% Sodium Sulfadiazine	5% Sodium Sulfacetimide
7.1	15.1	26.0
8.0	10.3	33.0
10.0	9.1	34.7
6.0	12.0	27.8

TABLE 17—*Results of Application of 10 Per Cent of Sodium Sulfadiazine and 10 Per Cent Sodium Sulfacetimide in Rabbit Eyes Burned with Mustard Gas Twenty-Four Hours Previously*

Milligrams of Sulfonamide Compound per 100 Cc of Aqueous Humor			
10% Sodium Sulfacetimide		10% Sodium Sulfadiazine	
O D Ointment	O S Drops	O D Ointment	O S Drops
50	120	10	32
42	70	17.6	30.5
63	84	18.6	34.2

Table 17 demonstrates that solutions allow more rapid penetration than ointments.

#### EVALUATION OF RESULTS

These studies demonstrate that the intraocular penetration of locally applied sulfonamide drugs is influenced by many factors.



The sulfonamide compound itself makes a difference. Sodium sulfamezathine produced the highest intraocular concentrations of sulfonamide in the normal rabbit eye, and sodium sulfacetimide, in the inflamed eye. Microcrystalline preparations did not give rise to significantly higher values than the macrocrystalline forms in the time intervals tested.

The alkaline salt of each sulfonamide compound produced higher intraocular values than the less soluble acid preparation.

The vehicle chosen made a real difference. Solutions allowed more rapid penetration than ointments. Ointments differed in this respect when applied to an inflamed and partially denuded cornea. An oil in water type of base allowed greater intraocular penetration of an inflamed and denuded cornea than did a water in oil type. However, the type of ointment was not an important factor in the presence of a normal cornea. Klein<sup>2f</sup> has shown that an oil in water type of base is a better ointment for intraocular penetration of other drugs, as well as of the sulfonamide compounds.

Although the concentration, 5, 10 or 20 per cent, made no real difference in the presence of a normal cornea, it was significant when the cornea was damaged. The results showed increasing concentrations in the aqueous humor with application of greater concentrations of each sulfonamide drug to the cornea burned with mustard gas.

Detergents increased the intraocular penetration of all sulfonamide compounds, both in the normal and in the inflamed cornea.

Most striking of all factors influencing intraocular penetration of locally applied sulfonamide drugs was the state of the cornea. A multi-fold increase in penetration occurred with each sulfonamide compound in the presence of an inflamed and partially denuded cornea.

Other factors not included in the experimental studies must be considered in selecting a sulfonamide drug for local administration.

The  $p_H$  of the tears usually is about 7.<sup>9</sup> Theoretically, it would be desirable to have a preparation of the same  $p_H$  as the tears, other factors being equal. Sodium sulfacetimide in 10 per cent concentration has a  $p_H$  of approximately 8, whereas the same concentrations of sodium sulfadiazine, sodium sulfapyridine, sodium sulfathiazole, sodium sulfamerazine and sodium sulfamezathine have a  $p_H$  of approximately 10. This may not be an important factor, as the tears have a rapid buffering action. Twenty medical student volunteers who were tested for subjective symptoms with instillation of a solution of 10 per cent sodium sulfadiazine in one eye and 10 per cent sodium sulfacetimide in

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<sup>9</sup> Feldman, J. P.  $p_H$  and Buffers in Relation to Ophthalmology, *Arch. Ophth.* **17** 797 (May) 1937.

the other noted little difference in irritative properties of the two solutions. There were no objective changes. The ammonium salt of sulfadiazine, in 10 per cent concentration, has a  $p_H$  of 9.2, and the calcium salt, in 5 per cent concentration, a  $p_H$  of 8.5. The calcium salt is not soluble in greater than 5 per cent concentration. There is clinical evidence that the calcium preparation is as efficacious as the sodium salt.<sup>10</sup> This compound could be used if the  $p_H$  were a real objection to the utilization of the sodium salt. The same variation in the cation could be applied to other sulfonamide compounds with high  $p_H$  values for their sodium salts.

The sulfonamide drugs vary in the concentration required to halt bacterial growth in vitro. Though a drug may be an effective agent in a test tube, it may not be effective in vivo. However, if a drug is ineffective against a certain bacterium in vitro, it most likely will prove unsuccessful in combating a disease caused by that organism. According to in vitro studies with *Staphylococcus aureus* and *Escherichia coli*, sulfanilamide is less effective than sulfapyridine, which is about as effective as sulfacetimide. Sulfadiazine and sulfathiazole are more effective than sulfapyridine and sulfacetimide.<sup>11</sup> In other words, it requires much greater concentrations of sulfanilamide than of sulfathiazole to produce a similar bacteriostatic effect on a specific strain of *Staph aureus*. Sulfamezathine<sup>12</sup> and sulfamerazine are similar to sulfa-

<sup>10</sup> Nelson, C. T., and Spink, W. W. Calcium Salts of Sulfadiazine and Sulfathiazole, *Am J M Sc* **206**:315 (Sept.) 1943.

<sup>11</sup> Helmholtz, H. F. Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetimide and Sulfapyridine on Bacteria Isolated from Urinary Infections, *Proc Staff Meet*, Mayo Clin **17**:529 (Oct 21) 1942. Wyss, O., Grubaugh, K. K., and Schmelkes, F. C. Non-Specificity of Sulfonamides, *Proc Soc Exper Biol & Med* **49**:618 (April) 1942. Cohn, A., Steer, A., and Seijo, I. Correlation Between Clinical and in Vitro Reactions of *Gonococcus* Strains to Sulfathiazole, *Am J M Sc* **203**:276 (Feb.) 1942. Spink, W. W., and Vivino, J. J. Sulfonamide-Resistant *Staphylococci*, *J Clin Investigation* **23**:267 (March) 1944. Rose, F. L., Martin, A. R., and Bevan, H. G. L. Sulfamethazine, *J Pharmacol & Exper Therap* **77**:127 (Feb.) 1943. Marshall, E. K., Litchfield, J. I., Jr., White, H. J., Bratton, A. C., and Shepherd, R. G. Comparative Therapeutic Activity of Sulfonamides Against Bacterial Infections in Mice, *ibid* **76**:226 (Nov.) 1942. Muir, R. D., Shamleffer, V. J., and Jones, L. R. Studies Pertaining to Antibacterial Activity of Sulfathiazole and Its Methyl Derivative, *J Bact* **44**:95 (July) 1942. Organe, E. S., and Polson, M. A. Comparison of in Vitro Inhibitory Effects and Bacteriostatic Activity, *Arch Int Med* **70**:777 (Nov.) 1942. White, H. J. Comparative Activity vs Coliform Bacteria in Intestines of Mice, *Bull Johns Hopkins Hosp* **71**:231 (Oct.) 1942. Rammelkamp, C. H. Present Status of Sulfonamide Therapy, *M Clin North America* **26**:1375 (Sept.) 1942.

<sup>12</sup> Schweinburg, F. B., and Yetwin, I. J. Sulfamethazine, *J Bact* **49**:193 (Feb.) 1945. Rose, F. L., Martin, A. R., and Bevan, H. G. L. Sulfamethazine, *J Pharmacol & Exper Therap* **77**:127 (Feb.) 1943. Schweinburg, F. B., and Yetwin, I. J. The in Vitro Action of Sulfamerazine, Phthalylsulfadiazine, Phthalylsulfamerazine and Phthalylsulfathiazole on Enteric Pathogens, *New England J Med* **230**:510 (April 27) 1944.

diazine in this respect. There is evidence that sulfamezathine is more effective than sulfadiazine *in vitro* against *Eberthella typhosa*, *Esch coli* and varieties of *Salmonella*.

However, it has been shown that in the ionized form all the sulfonamide compounds mentioned possess similar potency *in vitro*.<sup>13</sup> That is, at a high  $pH$  range (9 to 10) all sulfonamide compounds have their greatest dissociation and their greatest bacteriostatic activity and are fairly comparable.<sup>14</sup> At neutrality sulfadiazine is more readily dissociated than sulfanilamide, and thus more effective. Nevertheless, at any particular  $pH$  below 9 to 10, a high concentration of sulfanilamide would be more effective against a susceptible strain of *Staph aureus* than a very low concentration of sulfadiazine. In other words, for sulfacetimide, sulfanilamide or sulfapyridine to be effective, one should aim for higher concentrations in the infected tissues than are required for sulfadiazine, sulfathiazole or sulfamezathine.

While studying the mechanism of action of sulfanilamide, Woods<sup>15</sup> noted that small amounts of para-aminobenzoic acid would block the antibacterial effects of the compound. This suggests that the antibacterial activity is produced by interference with some metabolic function of the bacterial cell, as para-aminobenzoic acid is an essential growth factor for bacteria. Sulfonamide compounds differ in the quantities of para-aminobenzoic acid required to inhibit their activity. Almost six hundred times as much para-aminobenzoic acid is required to block sulfathiazole as to block sulfanilamide.

Other compounds found in the tissues also interfere with action of the sulfonamide drugs. Examples of these substances are methionine, peptone, aminoacetic acid and the products of tissue autolysis.<sup>16</sup>

Substances such as chloroazodin U S P ("azochloramid") have been incorporated in sulfonamide preparations prepared for local use to enhance the activity of the sulfonamide drug by destroying or binding the inhibitors.<sup>16</sup> Also, maintenance of high  $pH$  values with buffers prevents the great lowering of the  $pH$  that occurs with tissue autolysis. In this way, sulfonamide preparations are kept at higher  $pH$  levels, where they are more dissociated, and thus more active. Urea also aids by re-

13 Schmelkes, F C, Wyss, O, Marks, H C, Ludwig, B J, and Strandkov, F B. Mechanism of Sulfonamide Action, *Proc Soc Exper Biol & Med* **50** 145 (May) 1942.

14 Rose, H M, and Fox, C L, Jr. Ionization of Sulfonamides, *Proc Soc Exper Biol & Med* **50** 142 (May) 1942.

15 Woods, D. The Relation of *p*-Aminobenzoic Acid to the Mechanism of Action of Sulphanilamide, *Brit J Ophth* **21** 74 (April) 1940.

16 MacLeod, C M. Sulfonamides, *Ann New York Acad* **44** 447 (Dec 14) 1943, Factors Affecting Activity in Therapy of Local Infections, Lectures on Peace and War Orthopedic Surgery, American Academy of Orthopedic Surgeons, Ann Arbor, Mich, Edwards Brothers, Inc, 1943, p 316.

moval of necrotic tissue Urea may actually increase the bacteriostatic effects of the sulfonamide compounds<sup>16</sup>

The antibacterial action of the sulfonamide compounds has been shown to be inhibited by procaine<sup>17</sup> It is known that procaine can be hydrolyzed, with liberation of free para-aminobenzoic acid by esterases present in human tissues<sup>18</sup> Fortunately, the local anesthetics used in ophthalmology, such as cocaine, metycaine hydrochloride, tetracaine hydrochloride U S P, dibucaine ("nupercaine") hydrochloride and phenacaine hydrochloride U S P, show no such inhibition<sup>19</sup> Dibucaine and phenacaine hydrochloride may actually add antibacterial effect

Sulfonamide preparations possess a certain toxicity for ocular tissues There is evidence that they retard regeneration of corneal epithelium<sup>20</sup> This effect is barely detectable when the sulfonamide preparations are used as drops However, preparations in ointment or powder base are definitely harmful in this respect Powders are more dangerous than ointments, and ointments differ in their ability to retard epithelial regeneration Smelzer found a hydrous wool fat—petrolatum ointment to be less damaging in this respect than the vanishing cream (sodium stearate) type of ointment

An ideal ophthalmic ointment vehicle for sulfonamide compounds theoretically should retard epithelial regeneration minimally and be an oil in water type, if possible, in order to enhance penetration and maintain an alkaline  $pH$  as an aid in dissociation of the drug Of course it should not be irritating, should be of a proper consistency for ease of application and should not disappear too quickly from the conjunctival cul-de-sac

17 Peterson, O L, and Finland, M Sulfonamide Inhibiting Action of Procaine, *Am J M Sc* **207** 166 (Fe) 1944

18 Legge, J W, and Durie, E B The Antagonism Between Procaine and the Sulfonamides, *M J Australia* **2** 561 (Dec 26) 1942

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Attention has been directed recently to "sulfamylon" (para-[aminomethyl]-benzene sulfonamide) It is not inhibited by para-aminobenzoic acid <sup>21</sup> In 5 per cent concentration, it is more bactericidal in vitro against certain organisms and less toxic than streptomycin, in a concentration of 200 units per cubic centimeter, or than penicillin, in a concentration of 100 units per cubic centimeter In this concentration it produces no ocular irritation <sup>22</sup> Measurements of its intraocular penetration have not been reported Actual trials against experimental and clinical ocular infections have not been made

There are methods of applying sulfonamide preparations locally other than those mentioned Iontophoresis and corneal baths produce considerably higher intracorneal levels and concentrations in the aqueous humor than the former methods The best results in treatment of experimental infections have been attained with iontophoresis However, these two methods must be used either in the office or in the hospital and require special apparatus Many patients requiring local application of a sulfonamide preparation can be treated successfully without iontophoresis or corneal bath, particularly when the solutions and ointments containing the drug are properly selected and utilized

There exists a large literature describing the merits of local application of sulfonamide compounds in treatment of experimental and clinical ocular infections These articles are concerned mostly with cases of successfully treated conjunctivitis, blepharitis, keratitis and dacryocystitis <sup>23</sup> It is in such cases that local sulfonamide therapy will continue to be used

In considering the data listed in table 18, certain suggestions for the choice of a sulfonamide compound for local use may be made When the cornea is denuded and/or inflamed, apparently any of these drugs will penetrate adequately when applied either as drops or as an ointment Certainly, the sodium salt of almost any sulfonamide compound will penetrate sufficiently when applied by corneal bath or iontophoresis The low  $pH$  of solutions of sodium sulfacetamide would appear to be a factor in its favor

The only criticism that might be raised against the sodium salts of sulfadiazine, sulfapyridine and sulfamerazine is their high  $pH$  in 10 per

21 Mitchell, G A G, Reese, V S, and Robinson, C N Marfanil and Marfanil Protalbin, *Lancet*, 1 627 (May 13) 1944

22 Howes, E L Local Chemotherapy of Wounds, Surg, Gynec & Obst 83 1 (July) 1946

23 Rambo <sup>2a</sup> Johnstone <sup>2b</sup> Robson and Scott (footnotes 2c, d and e) Scott and others <sup>2f</sup> Dickson <sup>2g</sup> Bellows <sup>2h</sup> Thygeson <sup>2i</sup> Thygeson and Braley <sup>2k</sup> von Sallmann <sup>2l</sup> Alvaro <sup>2m</sup> Vorisek <sup>2n</sup> Simpson, G V Sulfadiazine in Treatment of Dacryocystitis of the Newborn, *Arch Ophth* 33 62 (Jan) 1945

TABLE 18 — *Usefulness of Various Sulfonamide Compounds for Local Therapy of Infections of the Anterior Segment of the Eye*

	Sulfanilamide	Sodium Sulfapyridine	Sodium Sulfacetamide	Sodium Sulfadiazine	Sodium Sulfathiazole	Sodium Sulfamerazine	Sodium Sulfamezathine
Approximate pH of 10% solution		10	8	10	10	10	10
Penetration into normal eyes with drops or ointment	Fair	Fair	Fair	Fair	Poor	Fair	Good
Penetration with iontophoresis and corneal bath in normal eyes	Good	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Penetration into eyes with inflamed and denuded corners of drops or ointment	Very good	Very good	Excellent	Very good	Very good	Very good	Very good
Relative bacteriostatic concentration, mg/100 cc of medium (Knight's) demanded in vitro against							
<i>Staph aureus</i>	14.0	3.0	2.0	0.60	0.30	0.6	0.6
<i>Esch coli</i>	15.0	2.9	2.8	0.65	0.65	0.5	0.5
Experimental evidence of effectiveness against infection of anterior segment, local application	Fair	Fair	Very good	Very good	Very good	No data to date	No data to date
Clinical evidence against ocular infection of anterior segment, local application	Good	Good	Good	Good	Good	No data to date	No data to date

cent concentration and their adequate, but not so high, penetrating values. Because of the high buffering ability of tears, the  $pH$  is not an important objection, and if it were the calcium salts could be used. The lower penetration is also not an objection, as the use of a detergent would insure higher intraocular concentrations. Detergents, however, must be used carefully, as repeated use may lead to superficial, although reparable, corneal damage.<sup>24</sup>

Chemical and experimental data on treatment of ocular infections with sulfamezathine, sulfamerazine and "sulfamylon" are meager. Frequent mention of ocular sensitivity to sulfathiazole occurs in the literature. Therefore, on the basis of available information, the sodium salt of sulfacetimide (now available commercially in 30 per cent concentration) would appear to be the drug of choice, because of its low  $pH$  and great penetrating ability, with sulfadiazine and sulfapyridine following in that order.

#### SUMMARY

1 The intraocular penetration of locally applied sulfonamide compounds is shown to depend on the following factors: (a) the physical form of the compound, (b) its solubility, (c) the vehicle, (d) the presence of a detergent and (e) the state of the cornea.

2 Other factors of importance in selecting a sulfonamide compound for local use are considered: (a) the  $pH$  of the preparation, (b) the bacteriostatic action *in vivo*, (c) the results against standardized experimental ocular infection, (d) the results against clinical infection in human eyes and (e) the toxicity of the preparation.

3 Suggestions are made as to the best sulfonamide preparation for local ocular use according to the available data.

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<sup>24</sup> Swan, K. C. Reactivity of Ocular Tissues to Wetting Agents, *Am J Ophth* **27** 1118 (Oct) 1944. Leopold, I. H. Local Toxic Effect of Detergents on Ocular Structures, *Arch Ophth* **34** 99 (Aug) 1945. Irvine, R. S. Wetting Agents and Detergents, *Am J Ophth* **29** 1317 (Oct) 1946.

Smith, Kline & French Laboratories, the Squibb Institute and the Schering Corporation supplied the drugs used in this study.

## MIOTIC AND ANTIGLAUCOMATOUS ACTIVITY OF TETRAETHYL PYROPHOSPHATE IN HUMAN EYES

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THE OCULAR effects of a new anticholinesterase chemical, tetraethyl pyrophosphate, have been investigated in several subjects with normal eyes and in several patients with glaucomatous eyes. Although the number of observations is small, the information obtained appears to be adequate for a qualitative characterization of the actions of this compound. A more quantitative experimental comparison of tetraethyl pyrophosphate with physostigmine and di-isopropyl fluorophosphate (DFP) and a clinical comparison with di-isopropyl fluorophosphate in glaucomatous and in atropinized eyes are to be reported subsequently.<sup>1</sup>

Tetraethyl pyrophosphate is a colorless, water-soluble and lipid-soluble, hygroscopic liquid of low volatility. It is the principal active ingredient of a more complex substance, commercial hexaethyl tetraphosphate (tri-diethyl phosphophosphate), which, because of strong nicotine-like action, was used in Germany during the war as an insecticide, substituting for natural nicotine, under the name of "bladan."<sup>2</sup> Tetraethyl pyrophosphate is being used increasingly in this country for the same purpose, under the name of "nifos." Pure tetraethyl pyrophosphate has several times as great biologic activity as has commercial hexaethyl tetraphosphate, but both substances are highly toxic to warm-blooded animals and produce extreme miosis. In the present investigation, the pure tetraethyl pyrophosphate has received principal attention.<sup>3</sup>

The few studies on the biologic action of tetraethyl pyrophosphate or of hexaethyl tetraphosphate which have thus far been published show that both compounds are highly effective inhibitors of cholin-

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From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary

1 (a) Cogan, D G, and Grant, W M To be published (b) Dunphy, E B, and Grant, W M To be published

2 Hall, S A, and Jacobson, M Hexaethyl Tetraphosphate and Tetraethyl Pyrophosphate Chemical and Physical Properties, *Indust & Engin Chem*, 40 694-699, 1948

3 The tetraethyl pyrophosphate and hexaethyl tetraphosphate were supplied by Dr J S Harris, of the Monsanto Chemical Company, St Louis



esterases, in fact, tetraethyl pyrophosphate is usually effective at lower concentrations than is physostigmine or di-isopropyl fluorophosphate<sup>4</sup> The lethal dose of systemically administered hexaethyl tetraphosphate and tetraethyl pyrophosphate in experimental animals is comparable to that of physostigmine<sup>5</sup> Ready penetration of the skin by hexaethyl tetraphosphate and tetraethyl pyrophosphate is indicated by a high lethal effectiveness after application to animal's skin<sup>5b</sup> A certain facility of penetration of these compounds into the eye, consistent with their known miscibility in water or oil, is suggested by reports of extreme miosis in rabbit eyes promptly following application of dilute solutions of hexaethyl tetraphosphate<sup>6</sup> Application of tetraethyl pyrophosphate in bland vehicles to the eyes of rabbits and guinea pigs likewise produces temporary maximum miosis without observable injury to the eyes<sup>1</sup> In fact, even pure tetraethyl pyrophosphate is not damaging to the corneal epithelium, as judged by usual clinical standards

The notable properties of cholinesterase-inhibiting action and ready penetration into the eye without injury suggested the possible usefulness of tetraethyl pyrophosphate in the treatment of glaucoma on the same basis as treatment with physostigmine or di-isopropyl fluorophosphate Accordingly, an assessment of the action of tetraethyl pyrophosphate on human eyes was undertaken

#### OBSERVATIONS ON NORMAL HUMAN EYES

For a preliminary estimate of the effectiveness of tetraethyl pyrophosphate as a miotic in the human eye, the minimal effective concentration for production of perceptible miosis was determined in several subjects Observations were made using aqueous saline solution, peanut oil, purified kerosene and liquid petrolatum as vehicles In the case of aqueous solutions, freshly mixed preparations were used, for tetraethyl pyrophosphate in water loses half its biologic activity in approximately seven hours at room temperature<sup>2</sup> In all tests, a drop of solution was placed in the conjunctival sac of one eye with the head held back and the lids held apart for approximately twenty seconds, whereas the companion eye was untreated and served as a control Differences

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4 (a) DuBois, K, and Mangun, G H Effect of Hexaethyl Tetraphosphate on Choline Esterase in Vitro and in Vivo, *Proc Soc Exper Biol & Med* 64 137-141, 1947 (b) Brauer, R W, Hodge, H C, and Ravin, H A The Inhibition of Cholinesterase Activity of Human and Canine Blood Plasma and Erythrocytes by Certain Phosphate Esters, *Federation Proc* 6 311, 1947 (c) Mangun, G H, and DuBois, K P Toxicity and Mechanism of Action of Tetraethyl Pyrophosphate, *ibid* 6 353, 1947 (d) Koppanyi, T, Karczmar, A G, and King, T O Effect of Tetraethyl Pyrophosphate on Sympathetic Ganglionic Activity, *Science* 106 492, 1947

5 (a) Hagan, E C, and Woodward, G Toxicological Properties of Hexaethyl Tetraphosphate, *Federation Proc* 6 335, 1947 (b) Deichmann, W B, and Witherup, S The Immediate Toxicity of Hexaethyl Tetraphosphate, Tetraethyl Pyrophosphate and Hexaoctyl Tetraphosphate to Rabbits and Rats, *ibid* 6 322, 1947

6 DuBois and Mangun<sup>4a</sup> Koppanyi and others<sup>4d</sup>

in pupillary size were determined periodically by inspection, and measurements were made with a standard entoptic pupillometer. The results of a series of such measurements are shown in the table, with those of similar measurements made using physostigmine sulfate and di-isopropyl fluorophosphate in 0.9 per cent solution of sodium chloride for purposes of comparison.

The data in the table indicate that the threshold concentration for miosis in human beings is of the same order for tetraethyl pyrophosphate as for physostigmine and di-isopropyl fluorophosphate when all are compared with the use of a common solvent, 0.9 per cent solution of sodium chloride. The data also indicate that tetraethyl pyrophosphate is absorbed with approximately equal effectiveness from a saline and from a peanut oil solution.

In these studies, the maximum concentration of tetraethyl pyrophosphate as applied to the normal human eye was 0.1 per cent in saline solution, which caused no immediate discomfort, but within three minutes provoked twitching of the lids and within seven minutes produced a difference in pupillary size of 1.5 mm with moderate spasm.

*Minimum Concentration of Drug Which Produced a Perceptible Difference in Pupillary Size*

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Tetraethyl pyrophosphate	
In peanut oil, 0.005%	(0.5 mm miosis in 1 of 2 subjects)
In purified kerosene, 0.001%	(0.5 mm miosis in 3 of 8 subjects)
In liquid petrolatum, 0.010%	(0.75 mm miosis in 1 subject)
In 0.9% sodium chloride, 0.003%	(1 mm miosis in 1 of 2 subjects)
Physostigmine sulfate	
In 0.9% sodium chloride, 0.001%	(0.5 mm miosis in 1 subject)
Di-isopropyl fluorophosphate	
In 0.9% sodium chloride, 0.005%	(0.5—1 mm miosis in 2 subjects)
<hr/>	

of accommodation for near vision. A maximum relative miosis of 2.25 mm with pronounced spasm of accommodation and aching of the eye and brow was present within fifteen minutes. At that time ocular tension was equivalent to 21 mm of mercury, the same as that in the companion, control, eye. Accommodation returned to normal only after four days, and relative miosis persisted for more than three weeks, although the difference in pupillary size was only 0.75 mm at the end of five days.

Eyes which received 0.01 per cent tetraethyl pyrophosphate, irrespective of the vehicle, showed within thirty minutes an average difference in pupillary size of 1 mm, with no conspicuous disturbance of accommodation. In most instances an anisocoria persisted for twenty-four hours after this dose of tetraethyl pyrophosphate. Some of the eyes which received miotic concentrations of the drug showed slight transient engorgement of conjunctival vessels. No discomfort from application of the drops was experienced, and there was no evidence of corneal damage at any time.

## OBSERVATIONS ON GLAUCOMATOUS HUMAN EYES

It was concluded from the observations on the effect of tetraethyl pyrophosphate on normal animal and human eyes that this drug might reasonably be tested on glaucomatous human eyes in concentrations as great as 0.1 per cent. Of the vehicles employed in the previous tests, it was concluded that peanut oil was most suitable for use with patients, since this vehicle permitted good absorption, caused no discomfort and was favorable to the stability of the compound. Purified kerosene was not chosen for this purpose, in spite of its apparent superiority with respect to absorption of tetraethyl pyrophosphate, only because some subjects noted a slightly unpleasant odor and taste after the application of this vehicle to the eye.

Of the patients on whom tetraethyl pyrophosphate was tried, 1 had absolute glaucoma, 4, secondary glaucoma, 9, chronic simple glaucoma, and 1, glaucoma with congenital aniridia. In most instances, trial of tetraethyl pyrophosphate was made after control of tension by means of other miotics had been found unsatisfactory.

## DESCRIPTION OF CASES

CASE 1—C F, aged 85, had absolute glaucoma of indeterminate duration in one eye, with tension of approximately 80 mm, which was uninfluenced by pilocarpine, methacholine and neostigmine. Tension was also unaffected by 0.1 per cent tetraethyl pyrophosphate or hexaethyl tetraphosphate, applied two to four times a day. When tetraethyl pyrophosphate was used more than twice a day, aching of the eye and brow was noted.

CASE 2—Z H, aged 75, with cataract, exfoliation of the capsule and glaucoma in the right eye, and glaucoma following intracapsular cataract extraction in the left eye, had had cyclodialysis, paracenteses and trephination on the left eye but no surgical treatment of the right eye. During the preceding ten months, 4 per cent pilocarpine nitrate had been used four to six times a day in both eyes, the tension remaining in the neighborhood of 30 mm in the right eye and 40 mm in the left. When medication was changed to use of 0.1 per cent tetraethyl pyrophosphate in both eyes twice a day for three weeks, the tension remained the same in the right eye and decreased only to approximately 35 mm in the left eye. The patient's only complaint in regard to the use of tetraethyl pyrophosphate was blurring and dimness of distance vision.

CASE 3—E F, aged 21, had had tension of about 60 mm most of the time during six months following dissection of a pupillary membrane due to an earlier traumatic cataract in one eye, the increased tension persisting in spite of trephination, iridotomy, iridectomy, paracentesis and use of 4 per cent pilocarpine nitrate. During treatment with 0.1 per cent tetraethyl pyrophosphate twice a day for two weeks, the tension varied from 45 to 48 mm. The conjunctival vessels became considerably congested, but the aqueous remained clear.

CASE 4—A G, a Negro aged 67, with neurosyphilis and primary atrophy of the optic nerve in one eye, had glaucoma with attacks of uveitis in the other eye. During the past three months the tension had stayed in the high forties in spite of treatment.

at different times with pilocarpine, methacholine and neostigmine, atropine, epinephrine and carbachol ("doryl") Trial of 0.1 per cent tetraethyl pyrophosphate twice a day for four days also produced no change in tension

CASE 5—L G, aged 72, had glaucoma in one eye following a complicated cataract extraction Under treatment with miotics, definite sensitivity to pilocarpine, methacholine with neostigmine, and probably also to physostigmine, appeared A cyclodialysis was done, after which the tension was maintained in the forties with use of 4 per cent pilocarpine nitrate, in the thirties with carbachol and in the high twenties with methacholine and neostigmine, all used four times a day Because of the multiple sensitivities, trial was made of 0.05 per cent tetraethyl pyrophosphate twice a day for a month With this drug, the itching, conjunctivitis and dermatitis rapidly disappeared, the patient had no unpleasant symptoms and the tension was maintained at 18 mm

CASE 6—M, aged 41, had chronic simple glaucoma in both eyes, which had been treated by trephination The anterior chambers were extremely shallow No miotic was required for the right eye, while 2 per cent pilocarpine nitrate maintained the tension at about 30 mm in the left eye A trial use of 0.1 per cent tetraethyl pyrophosphate in the left eye three times in one day was followed by a rise of tension to 46 mm, with rapid return to 30 mm on resumption of pilocarpine nitrate In order to determine whether the rise in tension had been due to an untoward effect of tetraethyl pyrophosphate or to insufficient miotic action, several days later two applications of 0.1 per cent tetraethyl pyrophosphate were made, in addition to the regular administration of pilocarpine A temporary rise of tension to 58 mm resulted On both occasions on which the tension increased, the anterior chamber became extremely shallow, but no cells or flare could be seen in the aqueous

CASE 7—S H, a Negro aged 64, had chronic simple glaucoma in both eyes, for which no operation had been performed Tensions were maintained in the middle thirties with use of 4 per cent pilocarpine nitrate five times a day A trial use of 0.1 per cent di-isopropyl fluorophosphate once a day had brought the tension to 21 mm, but the drug could not be tolerated by the patient on account of severe headaches, facial pain and nausea Again, with pilocarpine nitrate, as well as with the addition of 0.75 per cent carbachol, tension was in the thirties Trial instillations of 0.1 per cent tetraethyl pyrophosphate twice a day normalized the tension but caused considerable headache With the use of 0.05 per cent tetraethyl pyrophosphate twice a day for a month, only occasional mild headache was noted, and tension was kept in the low and middle twenties On two occasions, substitution of applications of an ointment containing 0.25 per cent physostigmine sulfate twice a day for five day periods was made for purposes of comparison, and tensions of between 27 and 31 mm were found

CASE 8—W S, a Negro aged 69, had chronic simple glaucoma in both eyes, for which no operation had been performed Tension (without treatment) was 48 mm, with use of 4 per cent pilocarpine nitrate four times a day, it was about 30 mm With instillations of pilocarpine continued in one eye and use of 0.1 per cent tetraethyl pyrophosphate twice a day in the other eye for five weeks, the tension was kept in the middle twenties in both eyes The patient noted blurring of vision and headache the first few times the drug was used, but not thereafter

CASE 9—R L, aged 80, had chronic simple glaucoma in both eyes, for which no operation had been performed With use of 4 per cent pilocarpine nitrate three times a day, tension was about 30 mm On administration of 0.1 per cent tetraethyl pyrophosphate twice a day for two days, the tension became 20 mm, but on account of headache and blurred vision, the use of pilocarpine was resumed, with return of tension to the original level

CASE 10—D A, aged 82, had chronic simple glaucoma in her only eye, in which tension was in the high thirties and had not been materially altered by treatment at different times during a year with 4 per cent pilocarpine nitrate, 1.5 per cent carbachol, 0.1 per cent di-isopropyl fluorophosphate or methacholine chloride and neostigmine sulfate. Permission for operation was refused, and tension rose to 48 mm on use of pilocarpine. The eye was white, the pupil small and the anterior chamber moderately shallow. One drop of 0.1 per cent tetraethyl pyrophosphate was instilled, and twenty minutes later the tension was 65 mm, without appearance of congestion. Treatment was continued with pilocarpine and physostigmine.

CASE 11—J M, aged 78, had absolute glaucoma in one eye, in the other eye there was cataract with exfoliation of the lens capsule and glaucoma, for which operation was refused, although the tension had varied from 30 to 50 mm during a year of medication with 4 per cent pilocarpine nitrate. The anterior chamber was deep. Without medication the tension was 62 mm, but with 1 drop of 0.1 per cent tetraethyl pyrophosphate it was brought to 37 mm in an hour. On a regimen of 0.05 per cent tetraethyl pyrophosphate twice a day, the tension was maintained between 34 and 40 mm, with no discomfort.

CASE 12—E C, aged 67, had chronic simple glaucoma in both eyes. With use of 4 per cent pilocarpine nitrate every four hours and 0.25 per cent physostigmine sulfate ointment at night, control of tension was good in one eye and inadequate (varying around 30 mm) in the other. The anterior chamber was very shallow in both eyes. With use of 0.1 per cent tetraethyl pyrophosphate three times a day, the tensions were maintained at essentially the same level as with the previous medication.

CASE 13—B C, aged 37, had had chronic simple glaucoma and repeated attacks of high tension, with dystrophy of the corneal endothelium and epithelial edema in one eye, for approximately three years. A trephination was done, but for nine months the tension had remained in the thirties in spite of treatment with 4 per cent pilocarpine nitrate and with epinephrine. Medication with 0.1 per cent hexaethyl tetraphosphate four times a day brought the tension within normal limits, and there was no discomfort. Trial treatment with 0.05 per cent tetraethyl pyrophosphate caused aching about the eye, but with use of a 0.025 per cent solution three times a day for six weeks the tension was kept between 13 and 25 mm, with no further discomfort except that from bullous keratitis, which had progressed despite the lowered tension.

CASE 14—M L, aged 38, had chronic simple glaucoma, congenital coloboma of the iris and choroid and cataract in both eyes. Without treatment the tension was in the neighborhood of 40 mm, while with use of 4 per cent pilocarpine nitrate, in addition to 1.5 per cent carbachol, several times a day it was in the high thirties. With 0.05 per cent tetraethyl pyrophosphate instilled three times a day, the tension was kept in the neighborhood of 20 mm or lower, and no discomfort was experienced.

CASE 15—F B, aged 5 years, had congenital nystagmus, aniridia, partial dislocation of the lens and tension of 30 to 40 mm in both eyes, with or without use of 2 per cent pilocarpine nitrate three times a day. One eye was then treated with 0.1 per cent tetraethyl pyrophosphate twice a day, giving a tension of 17 mm (under ether). For comparison, the other eye was treated simultaneously with 0.25 per cent physostigmine sulfate ointment twice a day, giving a tension of 21 mm (under ether). When miotics were discontinued for several days, the tensions became 32 and 30 mm (under ether), respectively.

#### COMMENT

Practically all patients for whom tetraethyl pyrophosphate was tried were examined on several occasions with the slit lamp biomicroscope, usually several days after treatment with the drug was begun.

No corneal damage was observed, nor was any perceptible aqueous flare or increase of cells in the aqueous observed to follow the use of the drug. The patient (case 6) who had the definite rise in tension following instillation of tetraethyl pyrophosphate on two occasions was examined twenty-four hours later, when the aqueous appeared normal. In an additional case, not reported here, in which tetraethyl pyrophosphate was used during convalescence from cyclodiathermy, the post-operative reaction subsided, and the aqueous became normally clear without delay. In no instance were systemic symptoms noted from application of tetraethyl pyrophosphate to the eye in the doses employed in the present study.

### CONCLUSIONS

From the observation reported here, it appears that tetraethyl pyrophosphate is effective as a miotic in the normal human eye in concentrations comparable to effective concentrations of physostigmine or di-isopropyl fluorophosphate. The duration of miosis induced with tetraethyl pyrophosphate is intermediate between that with physostigmine and that with di-isopropyl fluorophosphate.

In the treatment of glaucoma, tetraethyl pyrophosphate appears to be most effective in patients who respond appreciably to standard miotic drugs, such as pilocarpine, e. g., with lowering of their ocular tensions to the thirties. In several instances, lowering of tension was more effective at a dosage level of 0.05 to 0.1 per cent tetraethyl pyrophosphate twice a day than with use of 4 per cent pilocarpine nitrate several times a day. Comparison with physostigmine has not been adequately made, but in a case of chronic simple glaucoma (case 7) and in another of glaucoma with aniridia (case 15) an impression was obtained of some superiority of the drug over 0.25 per cent physostigmine sulfate ointment used twice a day. It is apparent from experience in case 5 that tetraethyl pyrophosphate may be used for patients who have sensitivities to other miotics.

Disadvantages of tetraethyl pyrophosphate which are shared in as yet undetermined degree with other anticholinesterase miotics, such as di-isopropyl fluorophosphate and physostigmine, are, most commonly, the symptoms of spasm of accommodation for near vision, dimness of vision and aching of the eye, particularly with excessive doses. These complaints appear to be usually absent or slight with administration of 0.05 per cent tetraethyl pyrophosphate twice a day, especially after the first few days of use, but may be pronounced with the 0.1 per cent solution, especially if this dose is administered more than twice a day. Less commonly, a rise in tension may be produced by tetraethyl pyro-

phosphate in certain eyes, as noted in cases 6 and 10. The features which may distinguish eyes responding in this way from other eyes have not been determined, but the extremely shallow chambers present in the case (6) in which rise in tension was most definitely due to tetraethyl pyrophosphate is suggestive of a mechanical predisposing factor. However, in other cases in which definitely shallow chambers were present (e g, case 12) the eye did not respond to the drug in this way.

#### SUMMARY

Tetraethyl pyrophosphate is comparable to physostigmine and di-isopropyl fluorophosphate in miotic activity in normal human eyes and is effective in lowering the tension in glaucomatous human eyes in which there is an appreciable response to standard miotics. Tetraethyl pyrophosphate may be used when there is local sensitivity to other miotics. In several instances, more effective lowering of tension has been obtained from administration of 0.05 to 0.1 per cent tetraethyl pyrophosphate in peanut oil twice a day than from use of 4 per cent pilocarpine nitrate several times a day. An excessive dose of tetraethyl pyrophosphate may cause aching about the eye, and in certain eyes the drug may cause an increase in tension.

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## EFFECT OF INSULIN HYPOGLYCEMIA ON THE CILIARY MUSCLE

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Ever since the introduction of insulin in the treatment of diabetes mellitus by Banting and Best, extensive studies have been made to determine the exact mode of action of insulin. Insulin lowers the blood sugar and stimulates the formation of glycogen in the liver. Recently, Price, Cori and Colowick<sup>1</sup> have found one fundamental function of insulin. They have demonstrated that the action of the enzyme hexokinase, which with adenosine triphosphate converts glucose to glucose-6-phosphate, may be inhibited in vivo or in vitro by anterior pituitary N F and that this inhibition can be counteracted by insulin.

In contrast to the action of insulin, anterior pituitary results in hyperglycemia and glycosuria. Another antagonist to insulin in the maintenance of the blood sugar level is epinephrine, which increases the blood sugar by mobilizing sugar from glycogen. When insulin is given in excess, changes in distribution of lipids and loss of chromaffin substance in the adrenal glands are found in various animals. This can be prevented by injections of epinephrine<sup>2</sup>. There is an increase of epinephrine in the circulating blood during insulin hypoglycemia<sup>3</sup>. Clinical and experimental evidences of increased secretion of epinephrine during insulin hypoglycemia are acceleration of the heart rate, dilatation of the pupils, flushing of the face and periodic apparent exophthalmos, with retraction of the lid in some stages.

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1 Price, W H, Cori, C F, and Colowick, S P. The Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, Letter to Editor, *J Biol Chem* **160** 633, 1945

2 Poll, H. Veränderungen der Nebennieren nach Einspritzung von Insulin, *Med Klin* **21**:1717, 1925, abstracted, *J.A.M.A.* **85**:2059 (Dec 26) 1925

3 Cannon, W B, McIver, M A, and Bliss, S W. A Sympathetic and Adrenalin Mechanism for Mobilizing Sugar in Hypoglycemia, *Am J Physiol* **69**:46, 1924. Tietz, E B, Dornheggen, H, and Goldman D. Blood Adrenalin Levels During Insulin Shock Treatments for Schizophrenia, *Endocrinology* **26**:641, 1940



In some stages of insulin hypoglycemia there are pinpoint pupils, pallor and salivation, all evidences of stimulation of the parasympathetic nervous system. During insulin hypoglycemia gastric secretion and motility are increased, and this increase can be inhibited by atropine or by section of the vagus nerve.<sup>4</sup> Poos<sup>5</sup> stated that Scheiner's test reveals an irritable condition of the ciliary muscle after injection of insulin. Schmidt<sup>6</sup> found that insulin caused no alteration in the equilibrium of the vegetative nervous system in any direction, and he observed no change in the refraction of the eye before, during or after insulin hypoglycemia.

The action of insulin is not yet fully understood. As the blood sugar falls after the administration of a large dose of insulin, many and varied signs and symptoms appear. Insulin hypoglycemia resembles anoxia and asphyxia in many ways.<sup>7</sup> It is difficult to determine whether the signs and symptoms are due to direct action of insulin, to hypoglycemia, to a lowered metabolism of the brain or to substances poured into the blood stream to counteract the insulin and raise the blood sugar. The symptoms vary at different stages of shock and in different types of persons.

#### PRESENT INVESTIGATION

This study was made on patients treated with insulin hypoglycemia for schizophrenia and other psychoses. This therapy is commonly called insulin shock although the patients do not go into true shock. Retinoscopic examinations were made before and during each treatment. A streak retinoscope at a distance of 1 meter was used. The following drugs were used individually to produce mydriasis or mydriasis and cycloplegia: 1 per cent paredrine hydrobromide ophthalmic,<sup>8</sup> 4 per cent, homatropine hydrobromide and 1 per cent atropine sulfate. The paredrine was instilled every ten minutes for six doses, the homatropine, every ten minutes for five doses, and the atropine, three times a day for three days.

There were no cases of delayed recovery. Usually the treatment was terminated by giving dextrose by stomach tube and occasionally by intravenous injection. The blood sugar, which was measured by the Folin-Wu method, varied from 21 to 60 mg per hundred cubic centimeters. The depth of shock did not depend so much on the level

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4 Quigley, J. P., Johnson, V., and Solomon, E. I. Action of Insulin on the Motility of the Gastro-Intestinal Tract, *Am J Physiol* **90** 89, 1929.

5 Poos, F. Augenerscheinungen bei erblichen Schwankungen des Blutzuckers, *Klin Monatsbl f Augenh* **84**.103, 1930.

6 Schmidt, R. Insulinschock und Auge, *Nervenarzt* **11** 615, 1938.

7 Gellhorn, E. Effects of Hypoglycemia and Anoxia on the Central Nervous System. Basis for Rational Therapy of Schizophrenia, *Arch Neurol & Psychiat* **40** 125 (July) 1938.

8 Paredrine hydrobromide ophthalmic is a 1 per cent solution of *p*-hydroxy-*a*-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved in merthiolate, 1 50,000.

of the blood sugar as on how long the blood sugar had been at a low level. There was a great variation in the reaction of patients to insulin. The retinoscopic examinations were made between two and three and one-half hours after the injection of insulin. The term "light wet shock" is used to denote a patient who is perspiring profusely but who can be aroused and answer questions, "deep wet shock," a patient who cannot be aroused and who will need to have dextrose administered by stomach tube or intravenously to bring him out of shock.

The refractive error, as found by retinoscopic examination, was translated into the spherical equivalent by adding the spherical and one-half the cylindrical value algebraically. The astigmatic error did not vary much unless it was necessary to hold the eyelids open for examination during shock.

With paredrine as a mydriatic, there was an increase in refractive power in 19 eyes during the shock period as compared with that determined by retinoscopic examination before shock. When the refractive power of an eye is increased, stronger minus lenses or weaker plus lenses are needed to correct the refractive error. Decreased refractive power (weaker minus lenses or stronger plus lenses) was found in 6 eyes. There was no change in 3 eyes. The increased refractive power varied from  $-0.12$  to  $-2.12$  D. The decreased refractive power varied from  $+0.12$  to  $+0.62$  D. The average change was  $-0.53$  D. This value was determined by adding all the changes algebraically and dividing the sum by the number of eyes tested. It was impossible to examine 1 patient during shock because the pupils could not be dilated with paredrine. The day before, without insulin, the pupils had dilated readily with paredrine, and the next day they dilated during shock with homatropine.

Of the eyes receiving homatropine cycloplègia, 28 showed increased refractive power varying from  $-0.12$  to  $-1.12$  D during shock. Twelve eyes showed decreased refractive power varying from  $+0.12$  to  $+0.75$  D. Ten eyes showed no change. The average change was  $-0.16$  D.

In the eyes receiving atropine cycloplegia, 5 eyes showed increased refractive power varying from  $-0.12$  to  $-0.37$  D during shock. Ten eyes showed decreased refractive power varying from  $+0.12$  to  $+0.50$  D. Five eyes showed no change. The average change was  $+0.09$  D.

If the patients are classified according to age, depth of shock and type of mydriatic used, striking differences are found. Patients over 40 years of age were not given atropine and were not allowed to go into deep wet shock.

In table 3 are listed all the changes in spherical equivalent, expressed in diopters, classified according to the type of mydriatic and the depth of shock. They are listed in order, from the greatest stimulation to the greatest relaxation of the ciliary muscle. The median is shown for each group.

TABLE 1—Data on Changes in Refractive Power After Insulin Hypoglycemia of 30 Patients

Case No	Age Yr	Sex	Insulin Dose, Units	Time, Hr	Degree of Shock* DWS (36 mg 100 cc)	Change in Spherical Equivalent D		
						Paredrine Hydrobromide	Homatropine	Atropine
1	25	F	140	3½	DWS		OD -1 12 OS -0 62	
			130	2½	DWS		OD +0 37 OS +0 75	
			140	2½	DWS		OD 0 OS +0 50	
			140	2½	DWS	OD -1 87 OS -2 12		
2	30	F	140	2½	DWS (39 6 mg 100 cc)		OD -0 56 OS -0 62	
			140	2½	LWS		OD 0 OS 0	
			140	2½	DWS	OD -1 62 O,S -1 50		
3	28	M	150	3	LWS (33 mg 100 cc)		OD -0 25 OS -0 25	
			200	3	DWS	Pinpoint Pupils		
4	51	M	20	3	LWS	OD +0 50	OS +0 50	
5	41	F	30	2½	LWS		OD -0 50 OS 0	
			140	2½	LWS		OD +0 12 OS +0 12	
			190 330	2½ 2	LWS LWS	OD -0 62	OS 0 OS 0	
7	28	M	180	3	LWS	OD 0	OS -0 12	
			150	2½	DWS	OD -1 00	OS -1 00	
			160	2½	DWS			OD +0 25 OS +0 25
8	33	F	110	2½	LWS	OD -0 12	OS +0 25	
			120	2½	DWS			OD +0 25 OS +0 25
9	36	M	100	2½	LWS		OD +0 37 OS +0 37	
			90	2½	DWS	OD -1 00	OS +0 25	
			20	3	LWS		OD -0 25 OS 0	
10	23	F	90	2½	LWS		OD -0 12 OS 0	
			100	2½	DWS	OD -1 50	OS +0 12	
			70	2½	LWS	OD +0 62	OS -0 37	OD -0 12 OS -0 12
12	31	F	20	3	Very light LWS	OD -0 25	OS -0 25	
			230	2½	LWS (27 mg 100 cc)	OD -0 50	OS -0 37	
13	49	F	160	3	LWS	OD +0 37 OS +0 37		
14	33	F	80	2½	DWS (30 mg 100 cc)	OD +0 18 OD +0 12	OS -0 18 OS 0	
15	15	M	170	2½	LWS			OD +0 37 OS +0 50
			180	3	DWS			OS +0 37
16	21	M	110	3	Very light LWS	OD -0 06		OS 0
17	19	M	100	2	LWS	OD -0 75		OS 0
18	20	F	100	2½	LWS	OD -0 50		OS 0
19	36	F	60	3	LWS	OD -0 12		OS 0
20	36	F	220	3	LWS	OD 0		OS 0
21	22	F	210	3	LWS	OD -0 75		OS -0 12
22	24	M	150	3	LWS	OD 0		OS -0 25
23	21	M	100	2	LWS	OD -1 75		OS -0 37
24	20	M	280	2½	DWS	OD -0 75		OS 0
25	25	F	180	2½	LWS	OD -0 25		OS +0 25
26	15	M	250	2½	LWS			OD +0 25 OS +0 12
27	31	F	70	2½	DWS (33 mg 100 cc)		OD -0 75 OS -0 50	
			40	3	DWS		OD -0 37 OS -0 12	

28	31	F	130	2½	DWS (27 mg 100 cc)	OD -0 25 OS -0 12
			100	2½	DWS	OD -0 25 OS -0 50
29	35	F	50	2	LWS	OD -0 62 OS -0 50
			60	3	DWS	OD -0 50 OS -0 50
30	17	F	40	2½	Very light	OD -0 37 OS +0 12

\*DWS indicates deep wet shock, LWS, light wet shock

TABLE 2—*Effect of Age, Depth of Insulin Hypoglycemia and Type of Mydriatic on Refractive Power*

Group	Age, Yr	No of Eyes	Depth of Shock*	Mydriatic or Cycloplegic	Average Change in Refraction, D
1	15-30	7	DWS	Paredrine†	-1 48
2	15-30	8	LWS	Paredrine	-0 50
3	31-40	2	DWS	Paredrine	-0 41
4	31-40	12	DWS	Homatropine	-0 31
5	15-30	10	DWS	Homatropine	-0 21
6	31-40	11	LWS	Homatropine	-0 11
7	15-30	11	LWS	Homatropine	-0 10
8	31-40	4	LWS	Atropine	-0 06
9	31-40	7	LWS	Paredrine	-0 05
10	15-30	9	LWS	Atropine	-0 03
11	41-51	6	LWS	Homatropine	+0 04
12	41-51	4	LWS	Paredrine	+0 15
13	31-40	2	DWS	Atropine	+0 25
14	15-30	5	DWS	Atropine	+0 27

\*DWS indicates deep wet shock, LWS, light wet shock

†Paredrine hydrobromide ophthalmic was used

TABLE 3—*Changes in Spherical Equivalent, Classified According to Type of Mydriatic and Depth of Shock\**

Paredrine Hydrobromide		Homatropine Hydrobromide		Atropine Sulfate	
Deep	Ophthalmic Light	Deep	Light	Deep	Light
-2 12	-1 75	-1 12	-0 62	0	-0 37
-1 87	-0 75	-1 00	-0 50	+0 25	-0 25
-1 62	-0 75	-0 75	-0 50	+0 25	-0 12
-1 50	-0 62	-0 62	-0 37	+0 25	-0 12
-1 50	-0 50	-0 62	-0 37	+0 25	-0 12
-1 00	-0 50	-0 56	-0 37	+0 37	0
-1 00	-0 25	-0 50	-0 25	+0 50	0
-0 75	-0 25	-0 50	-0 25		0
+0 18	-0 12	-0 50	-0 25		0
	-0 12	-0 50	-0 25		+0 12
	-0 06	-0 37	-0 12		+0 25
	0	-0 25	-0 12		+0 25
	0	-0 25	0		+0 37
	0	-0 18	0		
	+0 12	-0 12	0		
	+0 37	-0 12	0		
	+0 37	0	0		
	+0 50	+0 12	0		
	+0 62	+0 25	0		
		+0 37	0		
		+0 50	0		
		+0 75	+0 12		
			+0 12		
			+0 12		
			+0 25		
			+0 37		
			+0 37		
			+0 50		

\*"Deep" and "light" indicate deep and light wet shock. Spherical equivalents are expressed in diopters

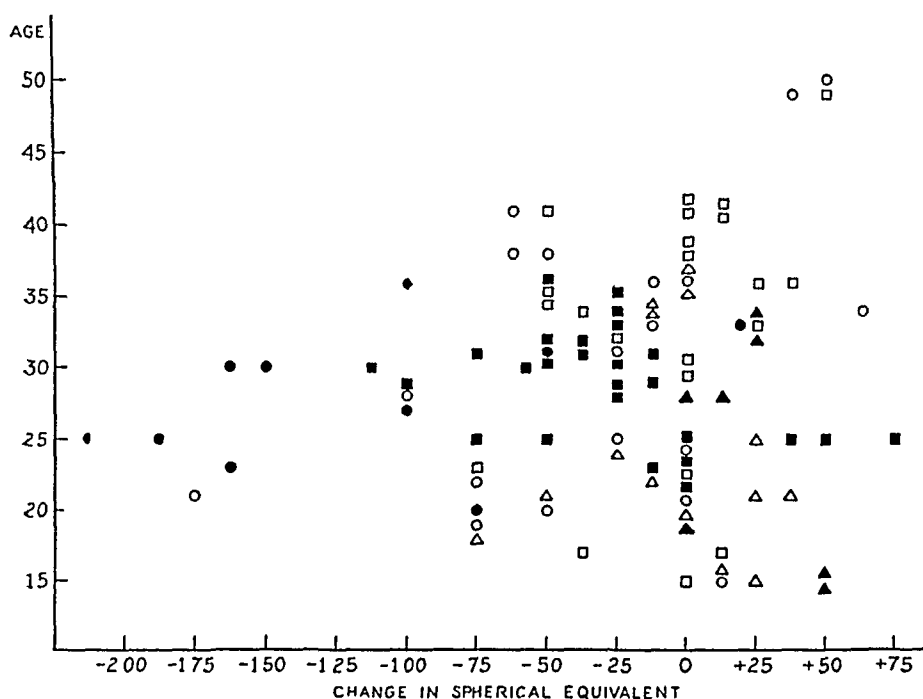


Chart 1—Changes in spherical equivalent classified according to age, type of mydriatic and depth of shock

In this chart and in chart 3, circles show values with pareдрine hydrobromide mydriasis during light wet shock (clear circles) and during deep wet shock (solid circles), squares, values for homatropine cycloplegia during light wet shock (clear squares) and during deep wet shock (black squares), and triangles, values for atropine cycloplegia during light wet shock (clear triangles) and during deep wet shock (solid triangles)

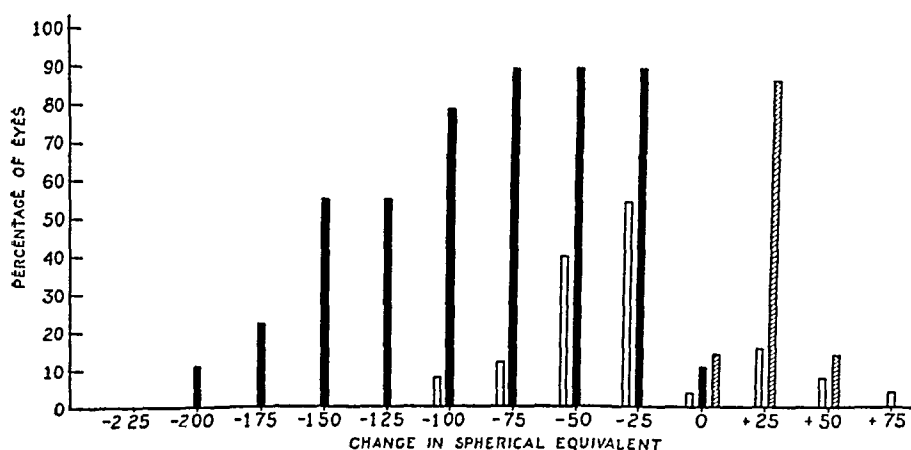


Chart 2—Percentage of eyes having as much as or more than the indicated change in spherical equivalent. For example, 89 per cent of the eyes under pareдрine mydriasis during deep wet shock had a change as much as or more than 0.25 D, while only 11 per cent had as much stimulation as -2.00 D

## COMMENT

It can be seen from the tables and charts that some of the patients with paredrine mydriasis had definite stimulation of the ciliary muscle and accommodation during insulin hypoglycemia, even up to 2 D. This was most evident in the youngest group and patients deepest in shock. Patients 20 to 30 years of age are easiest to throw into shock, the youngest patients have the greatest power of accommodation.

With homatropine cycloplegia a smaller percentage of eyes showed ciliary stimulation, and to a lesser degree, than with paredrine mydriasis. With atropine cycloplegia a still smaller percentage of eyes showed ciliary stimulation, and to a much less degree, than with homatropine cycloplegia. Some of the eyes showed relaxation of the ciliary muscle. This was most noticeable in deep wet shock with atropine cycloplegia.

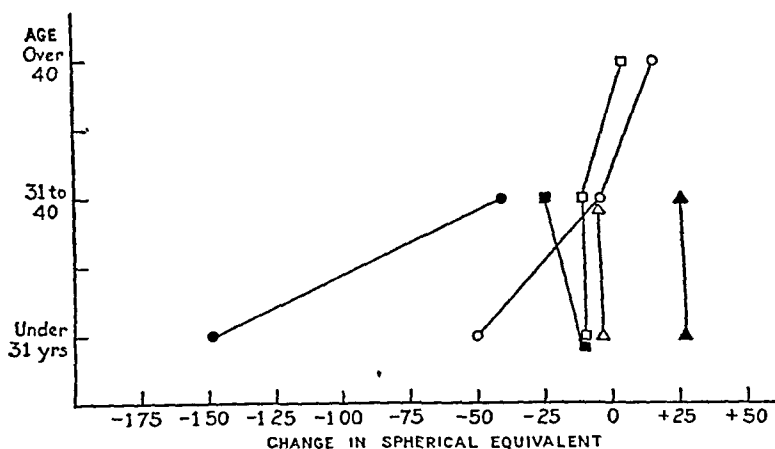


Chart 3—Graphic presentation of effects on refractive power of age, depth of insulin hypoglycemia and type of mydriasis (table 2)

Changes in deep wet shock during paredrine mydriasis are indicated by black areas, during homatropine cycloplegia, by clear areas, and during atropine cycloplegia, by cross-hatched areas.

This relaxation is not great enough to justify its removal entirely from the realm of possible error in examination. The removal of mental stimulation to accommodation during shock may be a factor. Many organs of the body are innervated by both parts of the autonomic nervous system. Does the ciliary body have a dual innervation? It is known that the thoracolumbar sympathetic system is stimulated during insulin hypoglycemia and that there is increased epinephrine in the blood.

The older the patient, the less the refractive power of the eye was increased with paredrine mydriasis during insulin hypoglycemia. This does not necessarily mean less stimulation of the ciliary muscle in patients of the older groups but may indicate that the ciliary muscle is less able to produce a change in refractive power, owing to decreased elasticity of the lens in older patients.

The results obtained by retinoscopic examination do not always agree with the results obtained by subjective examination, but the results of repeated retinoscopic examinations agree rather closely if the examining distance is kept constant. The change in the youngest group during deep insulin hypoglycemia is so striking with paredrine mydriasis and, when compared with the change with atropine cycloplegia, so different that it exceeds the error inherent in this type of examination.

The fact that the refractive change which occurs during insulin hypoglycemia can be abolished by atropine cycloplegia indicates that it is due to stimulation of the parasympathetic nervous system, which innervates the ciliary muscle. This observation is in agreement with other signs of stimulation of the parasympathetic system, namely, pinpoint pupil, slow heart rate, salivation and increased gastric secretion and motility.

The findings in this study support the observation of an irritable condition of the ciliary muscle during insulin hypoglycemia, as described by Poos. Schmidt's statement that there is no change in refraction during insulin hypoglycemia is essentially true if atropine is used as a cycloplegic. He did not describe his technic.

#### SUMMARY

Retinoscopic examinations were made on patients receiving insulin hypoglycemia treatment for schizophrenia and other psychoses. Paredrine hydrobromide ophthalmic, homatropine hydrobromide and atropine sulfate were used to dilate the pupils. Examinations were made before and during the hypoglycemia reaction. Definite stimulation of the ciliary muscle was found in some eyes when paredrine was used as a mydriatic. This was most pronounced in the youngest group of patients and was greatest during deep insulin hypoglycemia. Homatropine partially abolished the stimulation of the ciliary muscle during insulin hypoglycemia, and atropine almost completely abolished it, especially during deep insulin hypoglycemia. One patient had so strong a stimulation of the sphincter of the iris during the treatment that his pupils could not be dilated with paredrine, but they could be dilated at other times with paredrine and could be dilated with homatropine during treatment.

#### CONCLUSIONS

During insulin hypoglycemia there is in some subjects a definite stimulation of the ciliary muscle through the parasympathetic nervous system. This is most evident in young patients and during deep insulin hypoglycemia. Homatropine partially abolishes, and atropine almost completely abolishes, this stimulation.

## FRACTURES OF THE ORBITAL FLOOR

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In this paper I shall describe a not infrequently neglected deformity, present typical case reports of the condition in its various degrees of extent, evaluate the various methods of treatment which have been advocated and describe in detail the treatment which has proved most satisfactory in a group of 34 patients

Lukens<sup>1</sup>, reviewing the literature forty years ago, found 78 cases of traumatic enophthalmos and some nineteen hypotheses to explain its mechanism. Among the etiologic factors suggested were (1) indirect fracture of the orbital walls, (2) direct fracture of the orbital walls, (3) injury to Muller's orbital muscle, (4) injury to the check ligaments, (5) rupture of Tenon's capsule, (6) atrophy of orbital tissue due to injury of the sympathetic or trigeminal nerves, (7) hemorrhage of the ophthalmic artery behind the ciliary body, (8) minute hemorrhages in the nerve sheaths, particularly of the sympathetic nerves, (9) cicatricial contraction of orbital tissue following inflammation, (10) cicatricial adhesions of the eyeball, (11) cicatricial contraction of the extraocular muscles, (12) absorption of orbital fat due to the pressure incident to severe cellulitis, (13) similar pressure atrophy following orbital hematoma and (14) gross destruction of the orbital contents. Dislocation of the trochlea has also been postulated.<sup>2</sup>

With the passage of time, and particularly with improvement in roentgenographic technic, it is now felt by most observers that of the factors enumerated only the direct and indirect fractures of the orbital wall are significant and that the other factors play little, if any, part

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<sup>1</sup> Lukens, C. Traumatic Enophthalmos. Report of a Case, *Ophthalmology* 3:30, 1907

<sup>2</sup> Benedict, W. L., in Berens, C. *The Eye and Its Diseases*, Philadelphia, W. B. Saunders Company, 1936, p. 330



in producing the condition known as traumatic enophthalmos. Nevertheless, depressed fractures of the orbital floor are not infrequently overlooked, even when associated with more obvious depressions in the orbital rim. Particularly has this been true of severe injuries or war wounds in which the patient's condition is so critical that little attention is paid to what at the moment is of secondary importance. The residua of such injuries may later assume considerable importance, from the standpoint either of ocular dysfunction or of cosmetic appearance.

It has previously<sup>3</sup> been noted that the loss of an eyeball, by enucleation, when associated with a depressed fracture of the orbital floor, may lead to considerable difficulty in the satisfactory fitting of an ocular prosthesis. If the pathologic and mechanical problems are understood, logical measures can be taken to solve them. Usually the same principles will apply whether the fracture is of the orbital floor alone or whether there is an associated displacement of the orbital margin.

All the patients seen in this study had sustained injury several weeks to several months prior to my first observing them. Therefore the late treatment of such fractures is emphasized. For the sake of completeness, however, a review of the literature was undertaken to determine what measures have been used, and are currently in vogue, for the immediate treatment of fractures of the orbital floor and rim.

#### EARLY TREATMENT OF ORBITAL FRACTURES

Since the emergency treatment of such conditions will rarely fall to the ophthalmologist, most reports are those of general, oral, plastic or rhinologic surgeons.

In 1901 Le Fort,<sup>4</sup> after some forty experiments on cadavers, defined three main lines of weakness through the facial bones along which fractures were most likely to occur (fig 1). He applied blows of different degrees of violence to various parts of the face and by careful dissection noted the course of fracture lines. An unexpected degree of violence was required to produce a fracture.

1 The simplest fracture divided the maxilla above the alveolar processes, crossed the wall of the nose and the canine fossa, passed beneath the zygoma to the pterygomaxillary fissure and at times divided the pterygoid processes.

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3 DeVoe, A. G. Experiences with the Surgery of the Anophthalmic Orbit, *Am J Ophth* **28** 1346, 1945.

4 Le Fort, R. Experimental Studies upon Fractures of the Upper Part of the Face, *Rev de chir* **23** 208-227, 360-379 and 479-507, 1901, abstracted, *Brit Dent J* **71** 85, 1941.

2 Severer injury produced a fracture at a higher level, starting at the nasal bones and crossing the nasal processes of the maxilla and the inner wall and floor of the orbit to the region of the infraorbital canal. It then cut off the zygomatic process of the maxilla from the zygomatic bone, continuing backward to the pterygomaxillary fissure.

3 Increased violence produced a third type of fracture, in which the entire face was separated from the cranium. The fracture line crossed the nasal bones, the nasal process of the maxilla and the upper part of the inner wall of the orbit, opening the ethmoid cells nearly to the optic foramen. Near the posterior part of the *sphenomaxillary* fissure

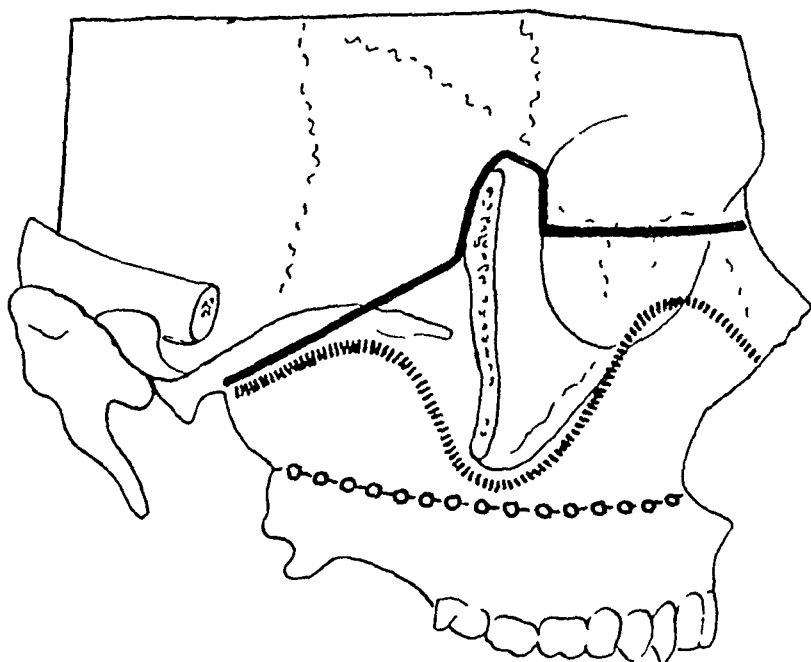


Fig 1—Fracture lines of Le Fort

the fracture line bifurcated, the front arm of the fracture crossing in the outer wall of the orbit to separate the zygoma from the frontal bone, while the posterior arm separated the pterygoid process near its base.

James and Fickling,<sup>5</sup> noting the investigation of Le Fort, went on to point out that the construction of the facial bones was such that a considerable resistance to injury was developed. This, they suggested, was due to the arrangement of areas of density in various bones, as at the orbital rim, and to the curves, buttresses and tie bars exemplified by the zygomatic arch, the pterygoid process and the palatine bone. A blow to the face is transmitted through these structures in a variety of directions and is dispersed so that no great force is directed to the cranium.

<sup>5</sup> James, W W, and Fickling, B W. The Structure of the Bones of the Face in Relationship to Fracture and Other Aspects of Facial Injuries, *Proc Roy Soc Med* 34 205, 1941.

and its enclosed vital centers. Firm and resistant structures lie on a light framework surrounding the nasal cavity and accessory sinuses. This complex is then attached to the base of the skull so as to absorb an applied force without transmitting it to the skull. The cushioning effect of the easily telescoped nasal-antral-ethmoidal structures will absorb much of a directly applied force. Furthermore, the localized increase in bone density around the teeth and eyes prevents damage to these structures. McIndoe<sup>6</sup> commented on the frequency with which the eye is left uninjured after a severe blow to the orbital region. Typically, lateral force applied to the zygomaticomaxillary area falls on the side of the cheek and is transmitted obliquely inward toward the cranial base. The amount of telescoping and impaction which occurs determines the degree of orbital deformity which follows. McIndoe stated that when moderate force only is applied the usual sites of clinical fracture will be found at the attachments of the frontosphenoidal, orbital and maxillary processes of the zygoma. The maxillary line of weakness is outward and downward through the infraorbital canal and the zygomaticomaxillary junction and backward along the floor of the orbit via the sphenomaxillary fissure. When severe violence is applied to this region, comminution of the zygoma occurs, with impaction into the antrum. A wide separation occurs at the frontomaxillary line of suture, and comminution of the thin orbital floor with prolapse of the orbital content into the antrum occurs.

It should be emphasized that the injuries described in the preceding paragraph are of the type due to a direct blow, such as are more commonly encountered in civilian life, the chief of which are a blow from a fist and injuries incurred in automobile accidents in which the face is thrown against the steering wheel, dashboard or windshield. Many military injuries, on the other hand, are due to explosive fragments and high velocity projectiles, which produce severe local destruction, in addition to expending their force along the lines of weakness previously detailed.

Many patients with orbital fractures, particularly those who have been in severe accidents, have multiple wounds, which may either obscure the orbital injury completely or reduce it to a position of minor importance, pending application of life-saving measures. Nevertheless, a certain proportion of persons so injured are in condition to withstand reduction of the orbital fracture. Most authors agree as to the desirability of this procedure, if possible, pointing out the not inconsiderable cosmetic blemish which may not be obvious until local swelling dis-

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6 McIndoe, A. H. *Diagnosis and Treatment of Injuries of the Middle Third of the Face*, *Brit Dent J* 71:235, 1941.

appears. Some feel that there is less likelihood of diplopia if reduction is rapidly accomplished.

Fractures which are most obvious, such as those involving the zygomatic arch and orbital rim, have often been repaired, and numerous reports are available. Although there is complete agreement concerning the desirability of early treatment, there is no such unanimity concerning the method by which this should be accomplished. Roberts<sup>7</sup> cited Duverney, in 1751, as being the first to mention fracture of the zygoma. Reduction was accomplished by pressure from within the mouth by fingers, a method which others have not found so successful<sup>8</sup> and which Lehmann<sup>9</sup> stated was impossible because of interference from the temporal muscle.

In 1897 Weir submitted 2 case reports<sup>10</sup> in which he described successful results following the elevation of fragments by an approach through the canine fossa into the antrum. This method, either with or without entry into the antrum, has been found satisfactory by a number of surgeons,<sup>11</sup> although the possibility of thus introducing infection has been mentioned by others.<sup>12</sup> In this connection, the point has been raised by a number of workers<sup>13</sup> that since injury to the antrum is present in all these cases, usually to be followed by hemorrhage and infection, treatment properly lies in the domain of the rhinologist. Entrance into the antrum and refracture of the depressed floor, followed by packing of the antrum, has also been suggested as a proper approach.

7 Roberts, S. E. Fracture of the Malar Zygomatic Arch, *Ann Otol, Rhin & Laryng* **37** 826, 1928.

8 Fracture of the Zygoma, Report from Charing Cross Hospital, *Lancet* **1** 186, 1872.

9 Lehmann, J. C. Depression Fracture of the Zygomatic Arch, *Zentralbl f Chir* **51** 2016, 1924, abstracted, *J A M A* **83** 1629 (Nov 15) 1924.

10 Weir, R. F. On the Replacement of a Depressed Fracture of the Malar Bone, *M Rec* **51** 335, 1897.

11 (a) Garner, J. R. An Operation for Reducing Depressed Fractures of the Malar Bone and the Zygomatic Arch, *Internat J Surg* **38** 411, 1925. (b) Evans, S. S. Fractures About the Orbit, *South M J* **26** 548, 1933. (c) Naftzger, J. B. Fractures of the Nasal Bones Involving the Nasal Accessory Sinuses, *Ann Otol, Rhin & Laryng* **37** 486, 1928. (d) Johnson, M. R. Depressed Fracture of the Orbital Rim, *S Clin North America* **24** 340, 1940. (e) Lothrop, H. A. Fractures of the Superior Maxillary Bone Caused by Direct Blows over the Malar Bone, *Boston M & S J* **154** 8, 1906. (f) Goldthwaite, R. H. Plastic Repair of Depressed Fractures of the Lower Orbital Rim, *J A M A* **82** 628 (Feb 23) 1924. (g) Eckhoff, N. L. Injuries of the Face, *Guy's Hosp Gaz* **54** 300, 1940.

12 (a) Lothrop<sup>11e</sup>. (b) Manwaring, J. G. R. Replacing Depressed Fractures of the Malar Bone, *J A M A* **60** 278 (Jan 25) 1913. (c) Gill, W. D. Fractures About the Orbit, *South M J* **21** 527, 1928.

13 Evans<sup>11b</sup>. Naftzger<sup>11c</sup>. Shea, J. J. The Management of Fractures Involving the Paranasal Sinuses, *J A M A* **96** 418 (Feb 7) 1931.

to the late treatment of fracture of the orbital floor,<sup>14</sup> but Gill<sup>15</sup> stated that it is best to resist the temptation to effect such a reduction and to be content with cosmetic improvement with cartilage and fascial implants. Spaeth<sup>16</sup> expressed agreement with this statement. In 1896 Matas<sup>17</sup> described a method of reducing fractures of the zygomatic arch, although he made no mention of existing deformities of the eye. This procedure consisted simply in passing a large curved Hagedorn needle threaded with silver wire behind the fragment and applying traction. Williams<sup>18</sup> made a similar report. Numerous other reports followed.<sup>19</sup>

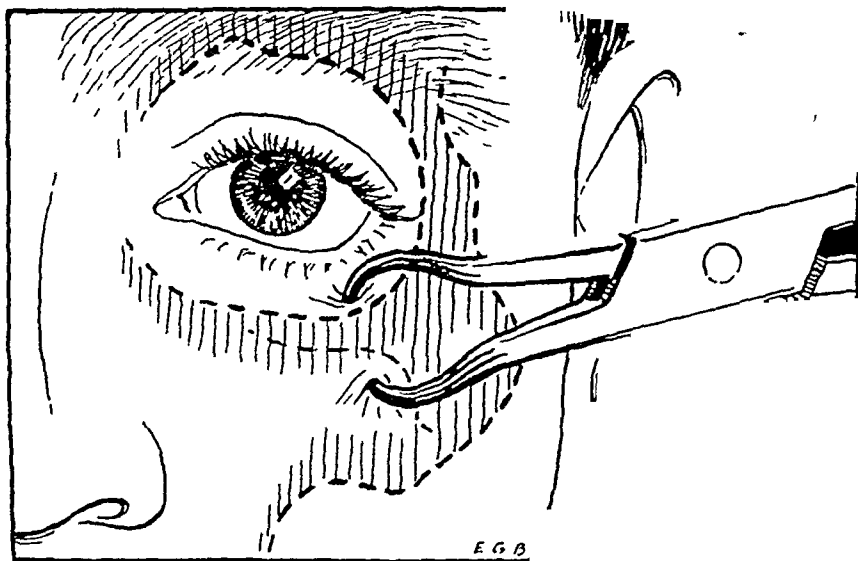


Fig. 2—Elevation of the orbital rim, with forceps

Open operation and reduction of the fragments have been described by some authors<sup>20</sup> and viewed with disfavor by others.<sup>21</sup> Manwaring,<sup>12b</sup>

14 Manual of Standard Practice of Plastic and Maxillofacial Surgery, Division of Medical Sciences, Committee on Surgery, National Research Council, Philadelphia, W B Saunders Company, 1942, p 220

15 Gill, W D Fractures Involving the Orbit, *M World* 56 663, 1938

16 Spaeth, E B The Immediate and Late Treatment of Injuries About the Orbit, *Surg, Gynec & Obst* 72 453, 1941

17 Matas, R Fracture of the Zygomatic Arch, *New Orleans M & S J* 49 139, 1896

18 Williams, S B Fracture of the Zygoma, *U S Nav M Bull* 5 341, 1911

19 (a) McCurdy, S L Depressed Fracture of the Malar Bone, with Report of Three Cases, *New York M J* 76 849, 1902 (b) Ellis, J A Fracture of the Zygomatic Arch, *Philadelphia M J* 3 467, 1899 (c) Gibson, C L Fracture of the Zygoma, *Ann Surg* 55 457, 1912 (d) Footnote 8 (e) Lehmann<sup>9</sup> (f) Lothrop<sup>11e</sup> (g) Goldthwaite<sup>11f</sup> (h) Manwaring<sup>12b</sup> (i) Codman, E A Depressed Fracture of the Malar Bone, *Boston M & S J* 162 532, 1910

20 Ellis<sup>19b</sup> Lehmann<sup>9</sup> Law, T B A Method of Dealing with Fractures Through the Infraorbital Margin, *M J Australia* 1 666, 1941

21 Codman<sup>19i</sup> Manwaring<sup>12b</sup>

using the ordinary "cow horn" forceps of the dentist, placed one point of the instrument over the orbital ridge and the other just under the margin of the body of the bone at its outer side. With a little pressure, the skin was penetrated and the bone grasped with any desired firmness. Disengagement and elevation of the bone were easily secured, and since there was no external wound no dressing was needed. Codman<sup>191</sup> described an essentially similar procedure, as did Gill<sup>22</sup> and Kazanjian<sup>23</sup>. These methods were applicable primarily to fractures involving a large piece of bone at the orbital margin. If a sizable portion of the orbital floor was attached, it was likely to be elevated with the rim. Usually such injuries produced no oculomotor disturbance (fig 2).

McCurdy,<sup>19a</sup> by screwing a coat hook into the fragment of bone, secured its elevation by traction. A more refined, corkscrew type of surgical instrument was utilized by Roberts.<sup>7</sup> Fixation of the parts after reduction has been effected does not appear to be necessary in the ordinary case, since there are no large muscle attachments to pull them out of place.

Simple fracture of the zygomatic arch or combined fracture of the arch and a portion of the inferolateral wall of the orbit may be most simply repaired by the method of Gillies, Kilner and Stone.<sup>24</sup> After a temporal incision in the hair line has been made, a periosteal elevator is then passed downward beneath the zygoma, and, with the use of the skull as a fulcrum leverage is exerted to raise the bony fragment into position. Subsequent fixation is not necessary (fig 3).

By any of these methods reduction of simple malar fractures is considered relatively simple. Little orbital deformity is present except at the rim, and there should be little or no displacement of orbital content with attendant ocular malfunction. Combined malar-maxillary fractures, such as were commoner in war injuries, are, however, another matter. Here, some type of splinting is required to retain comminuted fragments in place and to reelevator the orbital floor to its normal position. McIndoe stated that in cases of such fracture it is necessary to enter the antrum by a buccal approach and to elevate the fragments with gauze packing (fig 4).

Matthews<sup>25</sup> described the procedure in some detail, entering the antrum through the upper buccal sulcus, above the premolar and the

22 Gill, W. D. Fractures Involving the Orbit and Paranasal Sinuses, with Special Reference to Diagnosis and Treatment, *Texas State J Med* **27** 351, 1931 footnote 12c.

23 Kazanjian, V. K. Treatment of Injuries of the Upper Part of the Face, *J Am Dent A* **14** 1607, 1927.

24 Gillies, H. Kilner, T. P., and Stone, D. Fractures of the Malar-Zygomatic Compound, with a Description of the New X-Ray Position, *Brit J Surg* **14** 651, 1927.

25 Matthews, D. N. The Surgery of Repair Injuries and Burns, Blackwell Scientific Publications, London, Oxford University Press, 1943, p. 57.

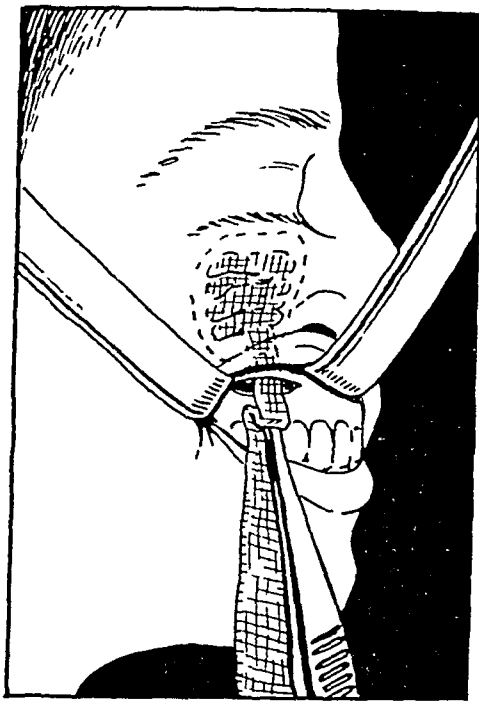
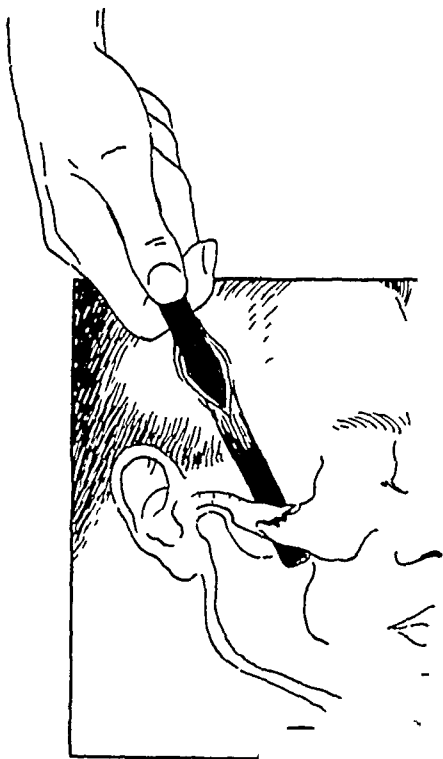


Fig 3 —Temporal approach for fracture of the zygoma

Fig 4 —Buccal approach for fracture of the orbital floor

first molar teeth. After the lower part of the anterior antral wall is resected, a lever is inserted and impaction of the fractured bone is relieved. The antrum is then packed firmly until the orbital defect is slightly overcorrected. This is considered to be a simple procedure if performed within ten days after the original injury but is considerably more difficult later. The pack is allowed to remain in place for two weeks before its removal, which must usually be done with the patient under general anesthesia. An intranasal antrostomy is performed at the same time in order to allow closure of the buccal wound and to safeguard against later antral infection. Johnson <sup>11a</sup> accomplished the antral packing by the insertion of a water-filled rubber balloon, which he allowed to remain in place for three weeks.

It is admitted that even immediate reduction by the aforescribed methods is not a guarantee against diplopia.

After fixation of the bony fragments in malunion, which may occur in several weeks, reduction is not usually considered possible. Replacement measures are then necessary. McIndoe stated that, in his experience, it is rare for diplopia to be overcome by subperiosteal insertion of bone or cartilage in the orbit.

Although most authors have stressed the importance of immediate treatment, Straith,<sup>26</sup> in a discussion of the management of facial injuries caused by motor accidents, warned against too hurried procedures of heroic nature. He stated that it is far wiser to delay than to attempt an emergency operation on a patient in poor condition, and in the presence of improper facilities. Serious hemorrhage is considered the only indication for immediate operation. A warning is also sounded to the effect that any serious facial injury should be treated as a potential fracture of the skull until proved otherwise.

The ophthalmologist is more likely to be called for consultation in late treatment of such cases than immediately. Frequently, diplopia is masked by edema of the lids and orbit and does not become annoying for several weeks after the injury. Again, intracranial damage may be so severe that immediate repair work must be postponed while life-saving measures are instituted. Such was the situation with the patients seen in the present series. All had been injured from several months to several years prior to my first seeing them.

#### LATE TREATMENT OF ORBITAL FRACTURES

Fracture of the orbital floor was recognized in 34 patients and an arbitrary division made into three groups: (1) patients with normal vision in the involved eye, (2) patients with the eye present but with defective vision and (3) patients in whom the eye had been removed.

GROUP 1—It is surprising how few symptoms may follow a fracture of the orbital floor. The patient may even be totally unaware of any deformity. Not infrequently, the patient has had an initial diplopia, which in the course of a few weeks or months may have disappeared. With a red glass, however, double vision can usually be elicited in some of the extreme positions of gaze. The remarkable compensatory power of the mechanism for binocular fusion has been noted by other observers,<sup>27</sup> particularly with relation to slowly progressive exophthalmos.

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<sup>26</sup> Straith, C. L. Management of Facial Injuries Caused by Motor Accidents, *JAMA* 108:101 (Jan 9) 1937, Automobile Injuries, *ibid* 109:940 (Sept 18) 1937.

(Footnotes continued on next page)



This power was again evident in the 6 patients seen in the present series who had a sudden displacement of the globe, experienced immediate double vision but were then able, in the course of a few months, to re-adjust their binocular vision so that they again saw singly. These patients were well adjusted, able to carry on their usual activities and completely uninterested in further treatment.

CASE 1 —A man aged 22 fell from a moving train and sustained a compound, comminuted, depressed fracture in the right frontal area associated with incomplete paralysis of the third and fourth nerves on the same side. On recovering consciousness after debridement of the craniocerebral wound, he immediately complained of double vision. This steadily became less troublesome and six months after the injury was limited to the upward field of gaze (figs 5 and 6).



Fig 5 (case 1) —Appearance following orbital fracture

The right palpebral fissure measured 7 mm and the left 9 mm, vision was 20/15 in each eye, and the exophthalmometer reading was 14 mm for the right eye and 16 mm for the left. Roentgenograms showed a depression of the orbital floor into the antrum unattended by injury to the infraorbital rim. A defect in the supraorbital ridge

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27 Eagleton, W P. Exophthalmos from Surgical Diseases, Especially as to Involvement of the Protective Retrobulbar Space, *Arch Ophth* **14** 1 (July) 1935. Lancaster, W B. Fifty Years' Experience in Ocular Motility, *Am J Ophth* **24** 492, 1941.

was associated with a fracture of the vault and the root of the orbit (fig 7) Measurements of muscular function revealed weakness of both elevator muscles of the right

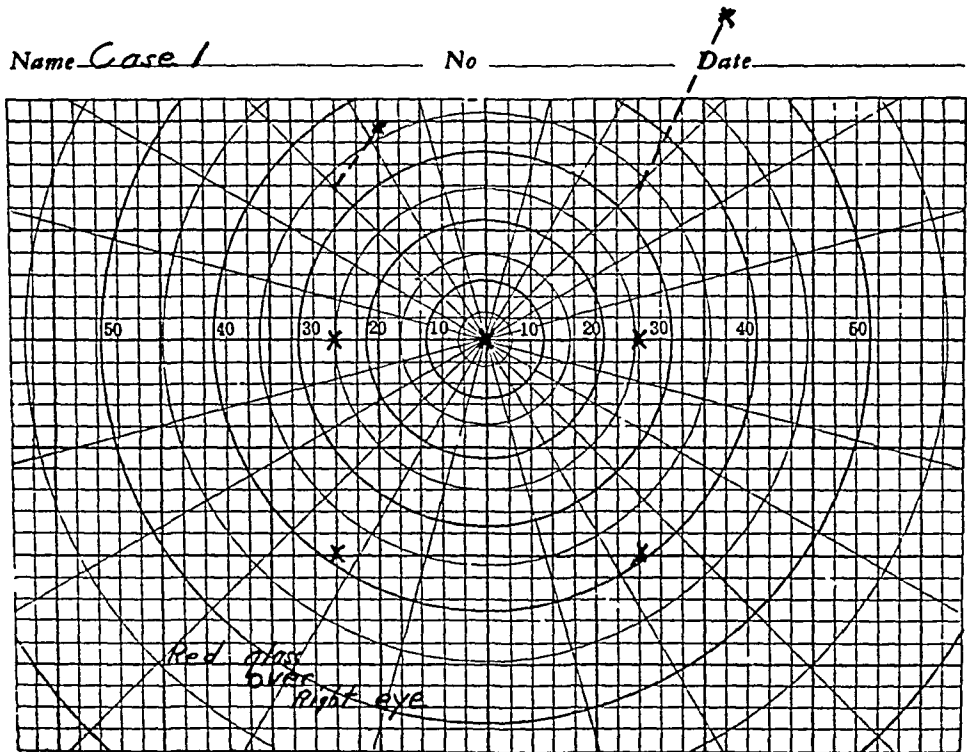


Fig 6 (case 1) —Plotting for diplopia, with red glass over the right eye



Fig 7 (case 1) —Roentgenographic appearance of the orbits

eye, particularly in the field of the superior rectus. When pressure was applied to the globe externally so as to raise it mechanically to its normal position, diplopia appeared

in all positions of gaze. Since diplopia was otherwise present spontaneously only in the upper fields, and not in the horizontal or the lower field, the patient was observed for an additional several months, during the course of which his symptoms became even less noticeable. Surgical intervention was not advised.



Fig 8 (case 2) —Appearance following orbital fracture

Name Case 2 No \_\_\_\_\_ Date \_\_\_\_\_

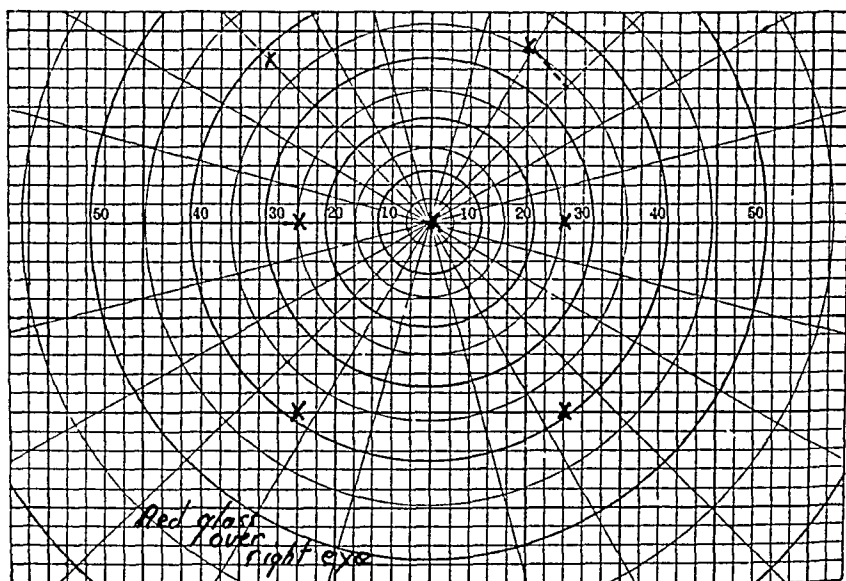


Fig 9 (case 2) —Plotting for diplopia, with red glass over the right eye

CASE 2 —While loading bombs in an airplane, the patient, aged 20, was grazed by a falling 500 pound (250 Kg) bomb, which knocked his head forward into another bomb. He received a deep laceration of the right brow, mild concussion and a linear fracture of the skull (fig 8).

As soon as the dressing was removed from the eye, the patient manifested severe diplopia on looking more than 30 degrees to the right or to the left. The double vision gradually subsided, so that six months later it was not disabling and was present only in his looking up to the extreme right or far down to the right (fig 9)

A slight palpable deformity was present in the supraorbital ridge. The right eye was 8 mm lower than the left and was somewhat enophthalmic. Vision was 20/15 in each eye, and examination otherwise revealed no abnormality except for anesthesia of the gums and teeth over the distribution of the right anterior and middle superior dental nerves. Stereoscopic roentgenograms of the orbit revealed well defined fracture of the floor of the orbit, unassociated with deformity of the orbital margin (fig 10)

Although it was felt that a cosmetic improvement could be obtained by surgical intervention, the patient became practically free from symptoms in the succeeding few months and did not desire further treatment.

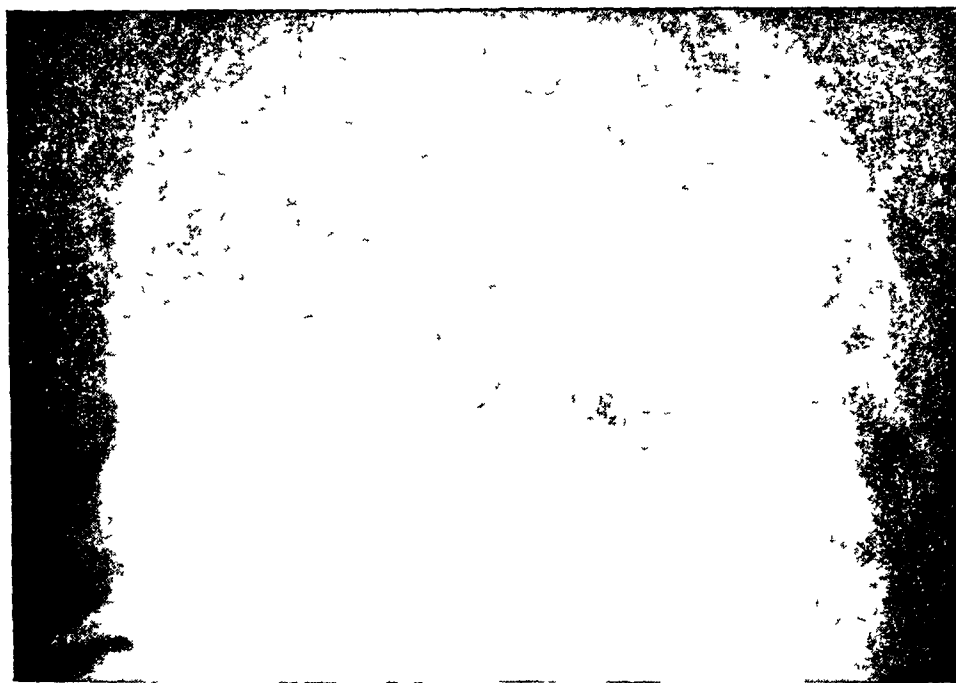


Fig 10 (case 2) —Roentgenographic appearance of the orbits

**REMAINING CASES**—The 4 other patients in this group were seen at intervals varying from two months to three years after the original injury. One of the patients was aware of double vision immediately after injury but two months later noted difficulty only in the extreme portions of the lower fields, and his diplopia was improving so rapidly that no surgical treatment was contemplated. Another patient, three months after injury, had no complaints, although diplopia could be elicited with a red glass in the extreme portions of the upper fields. The third patient, seven months after injury, noted double vision only on looking to the extreme left and had learned to compensate for this by turning his head to avoid the offending field. The fourth patient, seen three years after the original injury, had never been aware of double vision. All 4 men had objective signs of enophthalmos and roentgenographic evidence of a depressed fracture of the orbital floor.

*Comment*—Persons with good vision who have sustained this deformity and who have successfully readjusted their ocular muscular balance so that diplopia is absent or present only in the extremes of the unused fields need no further treatment. It is possible that reelevation

of the globe to its normal position would again produce diplopia, for which the patient might or might not be able again to compensate. Although not encountered in this series, cases exist in which severe fracture occurs, depression of the globe follows and the resultant diplopia is of a degree that renders spontaneous recovery impossible.<sup>28</sup> In such cases the logical treatment would seem to be an operative procedure which would elevate the globe to a more nearly physiologic position, so that the normally strong mechanism for binocular fusion would be in a position to take over. Such a case, in which the defect was repaired by subperiosteal insertion of bone from the iliac crest, was described by Converse.<sup>29</sup> Two weeks after operation the diplopia was said to have disappeared in all fields except in extreme upward gaze. Detailed ophthalmologic data were not given. Givner<sup>30</sup> also recently described notable improvement in a case in which repair was effected with preserved cartilage. Diplopia was not specifically mentioned, although strong hypotropia persisted and was thought to be due to injury of the inferior oblique muscle. Vision was 20/20 in each eye.

It is of some interest to note that in 1915 Murphy<sup>31</sup> replaced the outer wall of an orbit with an osteoperiosteal graft from the tibia so effectively that the eye was thereby "fully elevated to its former level." Previous attempts to elevate the eyeball by injection of paraffin had been notably unsuccessful.

**GROUP 2**—Eight patients, presenting varying degrees of deformity in association with fractures of the orbital floor, were found to have suffered severe loss of visual function. Since a blow severe enough to produce a large depression in the orbital floor will usually be sufficient to produce considerable intraocular damage as well, most patients with severe fracture will fall into this group or into group 3. Since the cosmetic appearance may be poor, many of these patients are anxious to have the globe replaced to as nearly normal anatomic position as possible. This correction is not always easy. The lines of fracture are usually united to the periorbita by scar tissue, and attempts to separate the tissue may either perforate the periorbita and allow herniation of orbital fat or penetrate the antral mucosa and so open an avenue of

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28 Ungley, H. G. and Suggit, S. C. Fractures of the Zygomatic Tripod, *Brit J Surg* **32** 287, 1944.

29 Converse, J. M. Two Plastic Operations for Repair of Orbit Following Severe Trauma and Extensive Comminuted Fracture, *Arch Ophth* **31** 323 (April) 1944.

30 Givner, I. Reconstruction of the Floor of the Orbit, *Am J Ophth* **29** 1010, 1946.

31 Old Compound Fracture of the Right Malar Bone Resulting in Loss of the External Wall of the Orbit, in Murphy, J. B. *Surgical Clinics*, Philadelphia, W. B. Saunders Company, 1915, vol. 4, p. 125.

infection I believe that herniation of the orbital fat is undesirable because of the ease with which its nutrition is impeded. Such interference may, in turn, cause atrophy of the fat, lessen the orbital volume and so add to the already existing defect. Perforation of the antral mucosa may or may not be harmful. In the majority of cases there is little, if any, infection in the antrum, and prompt healing by scar and callus formation will occur. Once the adhesions have been separated, it has been found easy to elevate the globe to a proper horizontal position. To effect the necessary forward protrusion is, however, not always simple. Particularly is this so in patients who have a concomitant dehiscence in the roof of the orbit. In these patients, insertion of material in the orbital floor is satisfactory up to a certain point, beyond which addi-

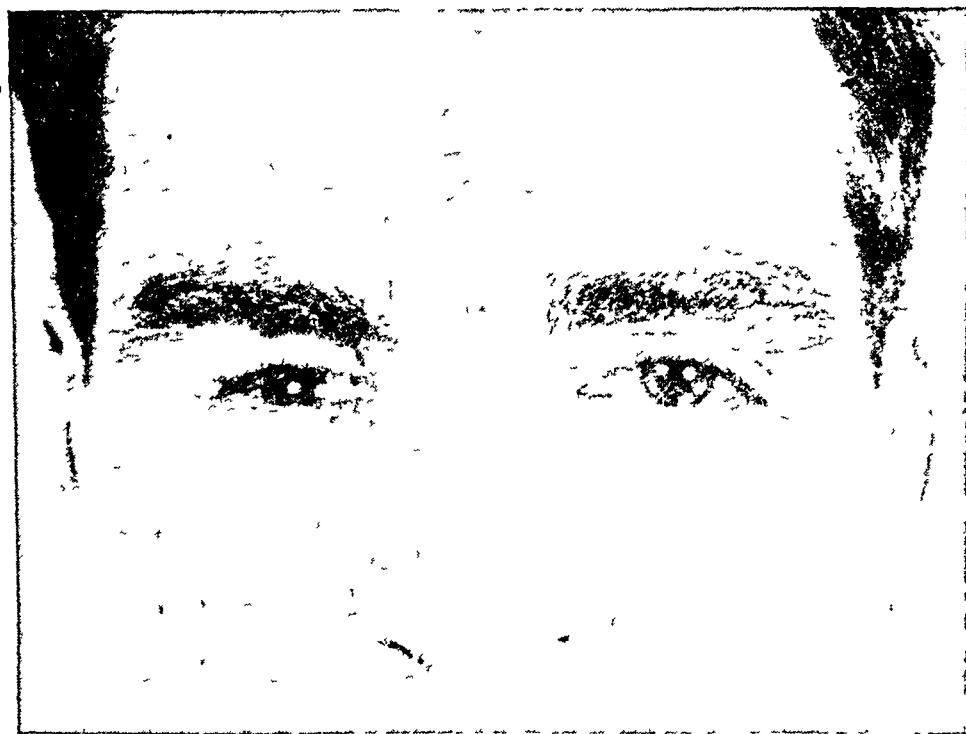


Fig. 11 (case 3) —Preoperative appearance

tion of more material does not cause further advancement of the globe but apparently displaces the orbital contents superiorly into the anterior cranial fossa.

**CASE 3**—The patient, aged 20, incurred a severe compound, comminuted, depressed fracture of both frontal and temporal bones when struck by fragments of a mortar shell. On recovery from his critical condition, and after having obtained a plastic repair of the deformity of the skull, the patient was anxious to secure a cosmetic improvement of the disfiguring enophthalmos incident to a depressed fracture of the orbital floor (figs 11 and 12). His condition was further complicated by the presence of a large hole in the roof of the orbit, allowing communication with the anterior cranial fossa. Traumatic chorioretinitis had reduced vision in the involved eye to 15/400 with correction. Accordingly, about seven months after his original injury, the floor of the orbit was exposed, the depressed fracture identified and preserved cartilage placed sub-

periosteally over the injured region. This subsequently was found to produce an under-correction, so that six weeks later the region was again exposed and tantalum ribbon packed posteriorly above the previously placed cartilage. Beyond a certain point, addition of more ribbon failed to produce protrusion of the globe and, in fact, caused re-



Fig 12 (case 3) —Roentgenographic appearance of the orbits



Fig 13 (case 3) —Postoperative appearance

traction. This was thought to be due to the dehiscence in the orbital roof and the probability that the orbital content was herniating into the anterior cranial fossa. Although the patient's condition is somewhat improved, the postoperative result is not considered successful (fig 13).

CASE 4—A man aged 28 was injured by a rifle bullet, which entered above the right malar region and lodged in the parieto-occipital area. On regaining consciousness one week later, he became aware of a homonymous field defect, the result of injury to the occipital lobe, as well as reduction of vision to 4/400 in the right eye, due to traumatic chorioretinitis. Two days after his injury an operation was performed, using the



Fig. 14 (case 4) —Preoperative appearance



Fig. 15 (case 4) —Roentgenographic appearance of the orbits

approach through the canine fossa, and the anterior walls of the maxillary sinus were exposed. The upper third of the anterior wall and the lateral third of the infraorbital ridge were observed to be fractured. The sinus was filled with old blood, fragments of bone and orbital contents, which had prolapsed laterally into the cavity. These fragments were removed, and a large intranasal opening was made into the inferior meatus. The postoperative course was uncomplicated. Examination two months after the orig-



mal injury (fig 14) revealed a palpable defect in the infraorbital ridge, depression of the right globe about 3 mm, divergence 14 degrees of arc and enophthalmos of 4 mm. Stereoscopic roentgenograms confirmed the depression of the orbital floor (fig 15).

In order to secure a cosmetic improvement, therefore, the floor was exposed and the periosteum elevated with some difficulty from the comminuted, irregularly healed fracture. Glass wool was inserted until the proper position of the globe had been obtained. The postoperative course was not remarkable and a satisfactory cosmetic result was obtained (fig 16).

**REMAINING CASES**—Of the 6 remaining patients in this group, 1 presented a picture similar to that of patient 3. In addition to a dehiscence in the floor of the orbit, there was a communication between the roof and the anterior cranial fossa. Implantation of preserved cartilage in the floor subperiosteally was successful in elevating the globe to its proper level but did not secure its forward protrusion, 6 mm of enophthalmos remaining unchanged. Addition of material was suggested, but the patient was satisfied with his cosmetic appearance and desired no further surgical treatment.



Fig 16 (case 4) —Postoperative appearance

Two patients with roentgenographic evidence of fracture of the floor did not present sufficient cosmetic blemish to warrant elevation of the floor, although 1 had a disfiguring loss in the inferior orbital rim, which was replaced with preserved cartilage.

The 3 remaining patients were transferred to hospitals closer to their homes after preliminary plastic work on the lids and adjacent structures was accomplished, but before the orbital repair could be carried out.

*Comment*—If a severe disfigurement is associated with a depressed fracture of the orbital floor and a nonfunctioning eyeball, it can be materially improved by mechanical elevation of the entire orbital content. In 1 case described, this was accomplished by subperiosteal insertion of preserved cartilage, supplemented with tantalum ribbon, in the other, by a similar use of glass wool. Any inert mass should accomplish the same result. Such procedures have been tolerated with a variety of materials and have not resulted in loss of motility of the eyeball. In

1 case, not included in this series, insertion of autogenous rib cartilage in the presence of preexisting conjunctival edema resulted in a severe orbital cellulitis. This eventually subsided, after systemic administration of penicillin, and the graft was not extruded. The globe, however, became frozen in the socket, and all motility was lost. It is possible, but not certain, that the antrum was entered during the dissection, allowing contamination of the orbital fat. Attention is also called to the additional complication which may arise if the orbital roof is damaged as well as the floor.

GROUP 3 —Twenty patients were observed who had a depressed fracture of the orbital floor associated with the loss of an eyeball. It is particularly easy to overlook such a fracture when the eye has been removed. The sulcus in the upper lid is thought to be one of the unavoidable complications which follow extensive wounds, and since many of these patients had had gunshot wounds it was logical to assume that destruction of orbital tissue had been caused by trauma from the missile. Clinically, the condition should be suggested by observation of a deep socket, either with or without the presence of an implant. All attempts to fit a satisfactory artificial eye, either glass or plastic, be it by use of the injection technic or by the addition of flanges or bolsters to the prosthesis, are doomed to failure. An unsightly loss of the superior orbital fold will persist. Routine roentgenographic examination in cases of this type will demonstrate frequently that the condition is due, at least in part, to an alteration in the orbital floor.

Numerous devices have been tried in an effort to correct this condition. As a rule, they depend on either or both of two principles: (1) use of a delayed orbital implant, such as Wheeler's grooved sphere implant,<sup>32</sup> or (2) subcutaneous insertion of a dermal graft, fascia lata or other material in the region of the depression. The former procedure is automatically sound, since it fills the deficiency in orbital content which has resulted from the enlargement of the orbit attendant on the displacement of the floor. The defect in the procedure is that only a small implant can be inserted as a delayed procedure and be retained. The volume of such an implant is small, rarely over 2 cc, which is insufficient except in the least severe deformities. The second procedure seems to me unsound, since it is not directed at the source of the difficulty. It will, however, improve the defect to a considerable extent.

Insertion of material directly into the orbit, but outside Tenon's capsule, is undesirable because such insertion requires dissection into orbital fat which, as has been previously noted, is susceptible to trauma,

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32 Wheeler, J. M. *Collected Papers on Ophthalmic Subjects*, New York, Columbia University Press, 1939, p. 427.

with resultant atrophy. The end result of such insertion may then be a cosmetic defect as great as, if not greater than, the original condition. The most logical approach to the problem, then, is the insertion of material into the orbit outside the periorbital. This provides a new floor for the orbit and, by raising its content, automatically obliterates the sulcus in the upper lid. Such a procedure was carried out on 9 of the 20 patients in this group and, in addition, was performed on 6 additional patients who presented the deformity of the upper lid but who did not have fracture of the orbital floor.

CASE 5—A man aged 24 was struck in the eye by a fragment of shell, receiving a severe laceration of the lid and such damage to the right globe that enucleation was performed. A large metallic foreign body was removed from the region of the greater wing of the right sphenoid bone and a primary repair of the lid performed at the same time. When first seen by me two months later (fig 17), the patient was observed to



Fig 17 (case 5)—Preoperative appearance

have notching of the lid at the site of the injury, shortage of tissue in the lower fornix and a deep socket without implant. Stereoscopic roentgenograms of the orbit revealed an old comminuted fracture of the left zygoma near the maxillozygomatic suture with a depression of the floor of the orbit into the antrum of 2 to 3 mm (fig 18).

As a primary procedure, a halving repair of the lower lid was performed and the patient fitted with a plastic artificial eye. Considerable depression of the upper lid was noted to persist. Consequently, about six months after his original injury, preserved cartilage, carved to fit and measuring 7 by 14 by 28 mm, was inserted subperiosteally in the floor of the orbit. With the fitting of another eye, a satisfactory cosmetic appearance was obtained (fig 19).

CASE 6—The patient was injured in a forced airplane landing, during which his head was thrown forward onto an instrument. The globe was shortly enucleated and a gold sphere implanted. Healing was uneventful, and careful roentgenographic studies



Fig 18 (case 5) —Roentgenographic appearance of the orbits



Fig 19 (case 5) —Postoperative appearance

were not made. Numerous attempts to fit an artificial eye, both glass and plastic, failed in securing a presentable result. Examination revealed an abnormally deep socket and an implant which could be palpated deep in the lower nasal quadrant. Fracture of the orbital floor was suspected and confirmed roentgenologically (figs 20 and 21).

About two years after the original injury, preserved cartilage was placed subperiosteally in the floor of the orbit. The site of fracture was demonstrated and observed to be firmly healed by callus. With the fitting of another plastic eye, considerable cosmetic improvement in the enophthalmos was obtained, although movement remained poor (fig 22).



Fig 20 (case 6) —Preoperative appearance



Fig 21 (case 6) —Roentgenographic appearance of the orbits

**OTHER CASES**—In addition to cases just described with demonstrable fractures of the floor, there exists another, rather large, group of cases in which there develops either early or late, after enucleation, a disfiguring loss of the fold in the upper lid. The mechanism of this occurrence is debatable but may be related to trauma of orbital

tissue during dissection, with subsequent atrophy. The defect may occur with or without the presence of an implant and is not rectifiable by any maneuvers of the maker of the artificial eye. After a trial of various methods to correct the deformity, such as delayed implantation of spheres or acrylic wedges of various shapes, as well as subcutaneous insertion of dermal grafts in the upper lid, it was thought worth while to attempt subperiosteal implantation in the floor. This was done in 6 cases, in 4 of which preserved cartilage was used and in 2 glass wool. The procedure was well tolerated and the immediate result satisfactory. Because of wartime conditions, none of the patients has been followed for more than a year and one half, admittedly too short a time on which to base positive conclusions. It is felt, however, that the procedure is worth further trial.

*Comment*—Any unusually deep socket in a case of anophthalmia should be viewed with suspicion and roentgenologic investigation of

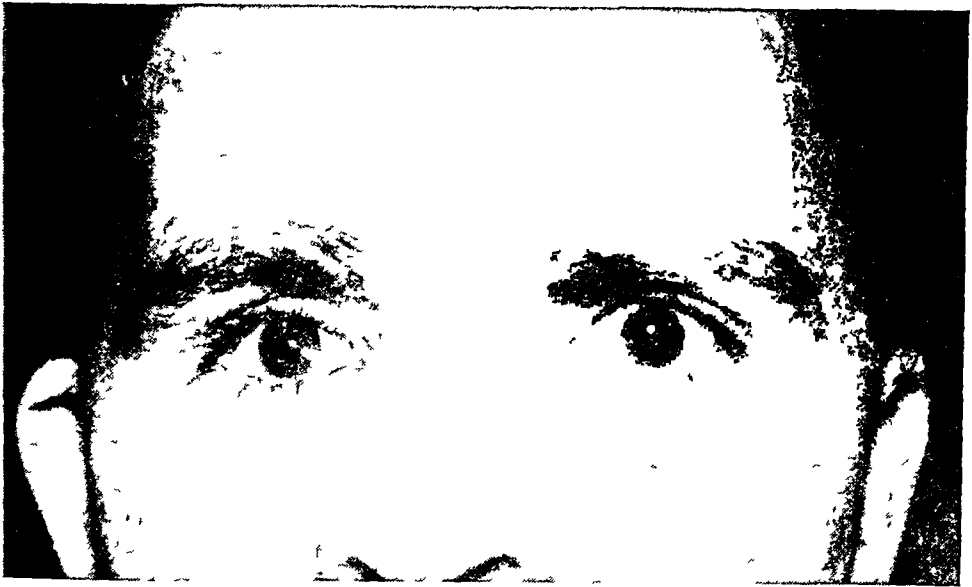


Fig. 22 (case 6) —Postoperative appearance

the status of the orbital floor undertaken. Particularly should this be done if an implant is present and found to be displaced inferiorly. Attempts at fitting artificial eyes by any technic will be unsuccessful in that apparent enophthalmos and loss of the normal superior orbital fold will persist. Considerable cosmetic appearance can be obtained by the insertion subperiosteally in the floor of the orbit of inert material to increase the orbital volume.

#### ROENTGENOGRAPHIC TECHNIC

As has previously been intimated, suspicion of the condition must precede its diagnosis. Not infrequently the patient has had routine roentgenograms of the skull. From these it has been impossible to evaluate the condition of the orbital floor. Pfeiffer<sup>33</sup> stated that failure

<sup>33</sup> Pfeiffer, R. L. Traumatic Enophthalmos, Arch Ophth 30:718 (Dec) 1943

to detect this condition is more often to be attributed to lack of correct technic than to inexperience or carelessness in interpreting the results. He emphasized the importance of proper centering and positioning so that a symmetric projection is obtained and pointed out that stereoscopic examination is essential. It should be noted that in every case of traumatic enophthalmos examined by Pfeiffer there was roentgenographic evidence of fracture of the orbit. Baltin reported similar observations<sup>34</sup>. Other observers have commented on the lack of reliability of roentgenograms in determining orbital fractures,<sup>35</sup> but in a properly centered stereoscopic projection the two orbits can be compared with considerable detail. All the patients in the present series had stereoscopic roentgenograms taken in both the Caldwell and the Waters position. All had lateral views, and many had roentgenograms of the optic canal as well. In my experience, the Waters position has been most valuable in determining the presence and the extent of the deformity in the orbital floor. Single roentgenograms were of little value, since they frequently yielded a picture hardly distinguishable from that of sinusitis. When seen stereoscopically, however, the downward bulging of the orbital floor into the maxillary sinus has been clearly demonstrable. The degree of prolapse of the orbital content has been said to be greater when the antrum is large. This is logical but was not specifically noted in this series.

Planigraphy has been said by some<sup>36</sup> to yield valuable information concerning various types of orbital fractures, but I have had no experience with this method.

#### TREATMENT

As previously noted, a number of patients seen late after an injury to the orbital floor will require no treatment because their mechanism for binocular fusion will have adjusted itself to the displacement of the globe, and cosmetic defect will not be great. In a great many others, however, treatment will be imperative.

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34 Baltin, M. M., and Svyadoshch, B. I. Roentgen Diagnosis of Blunt Injuries and Gunshot Wounds of the Orbit, *Vestnik oftal* 17:786, 1940, 18:306, 1942, abstracted, *Am J Ophth* 24:1338, 1941.

35 Gill, W. D. Fractures of the Facial Bones, with Special Reference to Involvement of the Paranasal Sinuses and Orbit, *South M J* 27:197, 1934. Hoffman, W., and Loepp, W. Value of Roentgenography in Injuries of the Orbit, *Arch f Ophth* 134:82, 1935, abstracted, *Am J Ophth* 18:894, 1935.

36 Culler, A. M. Fractures of the Orbit. The Demonstration of the Orbit by Planigraphy, *Tr Am Ophth Soc* 38:348, 1940. King, E. F., and Samuel, E. Fractures of the Orbit, *ibid* 64:134, 1944.

Earlier writers<sup>1</sup> expressed the belief that most attempts to overcome diplopia and restore the globe to its proper position would be futile, but recently reports have appeared in the literature demonstrating various methods of approach to the problem. Injection of paraffin was attempted and was soon discarded<sup>37</sup>. To overcome enophthalmos 'tenotomy of all four rectus muscles was said to be helpful'<sup>38</sup>. The use of diathermy, ingestion of potassium iodide and other ineffectual procedures have been described.

In 1941 Lyle<sup>39</sup> presented a group of 7 patients who had been greatly helped by operative procedures on the extraocular muscles. He also noted that most of these patients had been previously told that nothing could be done to correct their condition. At least four months was allowed to elapse between the time of injury and surgical repair. He found that the vertical deviations in this group were due to injury of either the superior rectus or the inferior oblique or of both, and in general, he carried out weakening procedures on the contralateral synergistic muscle. Three patients with hyperphoria of about 2 D were rendered orthophoric, and 3 others, with deviations of 10 to 20 D, were made practically so. One patient, with a deviation of 45 D, was not helped greatly. All operations were carried out with local anesthesia, without injection of anesthesia into the muscle, and with Maddox rod fixation on an overhead light. The use of prisms in cases of low error was suggested. There seems to be no question that relatively low degrees of error can be corrected if necessary by such methods, particularly when the deviation is due to injury of muscles or nerves rather than to severe displacement in the orbital walls.

The idea of mechanically raising a prolapsed globe to its proper position is not new. As has been noted, it was described by Murphy in 1915, but the statement has been made that cartilage placed immediately above the inferior portion of the prolapsed periorbital fails to produce a satisfactory result<sup>40</sup>. This has not been our experience or that of others<sup>40</sup>. The question also arises whether it is better to use autogenous

37 Darier, A. Therapeutics, in Pyle, W. L. *An International System of Ophthalmic Practice*, Philadelphia, P. Blakiston's Son & Co, 1910, p. 198.

38 Lagrange, F. *Medical and Surgical Monographs*, New York, D. Appleton & Company, 1918, vol. 4, p. 802.

39 Lyle, T. K. Some Cases of Post-Traumatic Diplopia Following Head Injury and Their Treatment, *Tr. Ophth. Soc. U. Kingdom* **61** 189, 1941.

40 Gill<sup>15</sup> Spaeth, E. B. *The Principles and Practice of Ophthalmic Surgery*, ed. 2, Philadelphia, Lea & Febiger, 1941, p. 73. Figi, F. A. Traumatic Scarring and Depressed Fracture of the Right Malar Bone and Orbital Border. Cartilage Implant, *S. Clin. North America* **12** 947, 1932. McIndoe, A. H. The Treatment of Old Traumatic Bony Lesions of the Face, *Surg., Gynec. & Obs.* **64** 376, 1937.



or preserved cartilage in such reconstructions Peer<sup>41</sup> recently reviewed the fate of such grafts and stated the opinion that autogenous grafts in adults continue to live, neither increasing nor decreasing in size, and that such grafts in infants will continue to grow, since cartilage early in life has not lost its growth potential Webster<sup>42</sup> also expressed the belief that it is better to use autogenous cartilage In several of the patients included in this series, I had occasion to operate a second time, two to four months after the original operation, either to readjust the position of the cartilage or to add more On these occasions biopsy specimens were taken of the previously placed grafts, both autogenous and preserved, and subjected to microscopic examination In none was there evidence of viable cartilage cells, and all showed beginning phagocytosis peripherally It may well be that, as Peer has suggested, these autogenous grafts were too thick or that the site of their implantation was lacking in the necessary vascularity and that diced cartilage would be more suitable<sup>43</sup> Be that as it may, it appears uncertain that any type of cartilage graft will endure permanently when buried subperiosteally in the floor of the orbit

For this reason, attempts were made to secure some easily obtained and well tolerated material Cancellous bone from the crest of the ilium has been recommended, but its use presents added difficulties to the procedure The use of fascial and dermal grafts offers the same objection as cartilage Acrylic wedges and plates<sup>44</sup> and inert metals, such as tantalum and "vitallium," have been used, but there is the objection to their employment that they must be largely performed to the anticipated size of the defect and are not easily adjusted on the operating table In the present state of knowledge, acrylics are not tolerated by all human beings, although it is probable that new methods of curing and preparation will shortly correct this Tantalum also has the disadvantage of developing high temperatures by induction, and should the patient subsequently receive diathermy he might be badly burned In 1 case in this series, however, tantalum ribbon was used without complication

It was felt that the ideal material for filling orbital defects would be some form of wool or packing Recent reports concerning the use of

41 Peer, L A Cartilage Grafting, *S Clin North America* **24** 404, 1944

42 Webster, J P Some Procedures for the Correction of Ear Deformities, *Tr Am Soc Plastic & Reconstruct Surg* **13** 123, 1944

43 Peer, L A Diced Cartilage Grafts New Method for Repair of Skull Defects, Mastoid Fistula and Other Deformities, *Arch Otolaryng* **38** 167 (Aug) 1943

44 Souders, B F Elevation of Orbital Contents with Plastic Plates, *Cirle General Hospital Military Ophthalmological Meeting Procedures*, November 1945, p 28 Sherman, A E Choice of Procedure in Ophthalmic Plastic Surgery, *ibid*, November 1945, p 121

glass wool as suture material<sup>45</sup> suggested its use in the orbit. To date, it has been used in 4 of the cases reported in this series and has been well tolerated. In 1 other case, seen elsewhere, the material was inserted subcutaneously to build up an orbital rim. A sterile accumulation of serum developed immediately after operation but has subsided over a period of several months. Whether the material will warrant further use remains to be seen. It is, however, easily handled and inserted into the irregular crevices frequently found in a depressed fracture of the orbital floor.

#### OPERATIVE TECHNIC

An incision, 15 to 20 mm, is made in the crease of the lid centrally over the inferior orbital rim and the dissection carried down through the orbicularis to the orbital rim about 5 mm below its margin. With a knife, the periosteum is incised and its elevation with periosteal elevators begun. The periosteum will be found firmly adherent at sites of fracture and along the orbital fissures but can usually be dissected free nearly to the orbital apex. As much packing is then inserted into the orbit as is necessary to produce the proper position of the globe and fullness of the upper lid. The periosteum is then tightly closed with fine nylon (000000), the edges of the skin are approximated and a pressure dressing is applied. If an artificial eye is worn, it is put in place before application of the dressing. The only postoperative complication which has been encountered to date is anesthesia over the distribution of the zygomatic nerve for several weeks, presumably due to the stretching of that nerve in the orbit during the elevation of the periosteum. External deformity is negligible, although when a large amount of material has been inserted temporally there is a tendency for the outer canthus to be raised. In some fractures, particularly those with coexisting separation of the zygomaticofrontal synchondrosis, this is an asset rather than a defect. It is believed desirable not to perforate the periorbita and allow the orbital content to herniate because of the ease with which such tissue is devitalized. Entry into the antrum will also eventually occur, but since in these old injuries there is little inflammatory residue, orbital cellulitis is unlikely to develop and prompt healing with scar tissue will occur. As a rule, postoperative reaction is minimal, and the dressings can be removed within a week. If, months or weeks later, it becomes apparent that insufficient correction has been accomplished, there is no contraindication to repetition of the procedure.

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<sup>45</sup> Scholz, R. P., and Mountjoy, P. S. Fiberglas Suture Material. Preliminary Report, *Am J Surg* 55:619, 1942.

## SUMMARY

Thirty-four cases of fracture of the orbital floor were observed and the following conclusions drawn

1 The immediate care of such fractures will rarely be an ophthalmologic problem because of the multiplicity of the injuries, often of a vital nature, which usually accompany the condition. A review of the literature has been made to determine the measures most frequently used in immediate treatment.

2 When weeks or months have elapsed since the original injury, the ophthalmologist is the one best fitted to carry out reparative work.

3 Such repair may take the form of operation on the extraocular muscles or may require substitution of inert material in the orbital floor in order to restore orbital volume or elevate the globe to a proper position.

4 In anophthalmic patients the cosmetic appearance can often be improved by restoration of the orbital floor.

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## DEVELOPMENT OF CHANGES IN VISUAL FIELDS ASSOCIATED WITH GLAUCOMA

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IT IS GENERALLY admitted that a comparative study of the visual field is the most important index of the progress of the disease in a given case of glaucoma. Since there is considerable variation in the evolution of the field defects in individual cases, it was deemed advisable to undertake a survey and classification of a large sample of unselected cases. The material for the present study consists of approximately 2,000 visual fields representing 350 patients with glaucoma from private practice.<sup>1</sup>

By appropriate grouping of these fields, it was found possible to follow the evolution of the various components of the field defect. An attempt was then made to formulate a hypothesis which would adequately explain the pathogenesis of the elements of the glaucoma field. These field studies have been carried out by a uniform method over the past fourteen years. The technic will be described later.

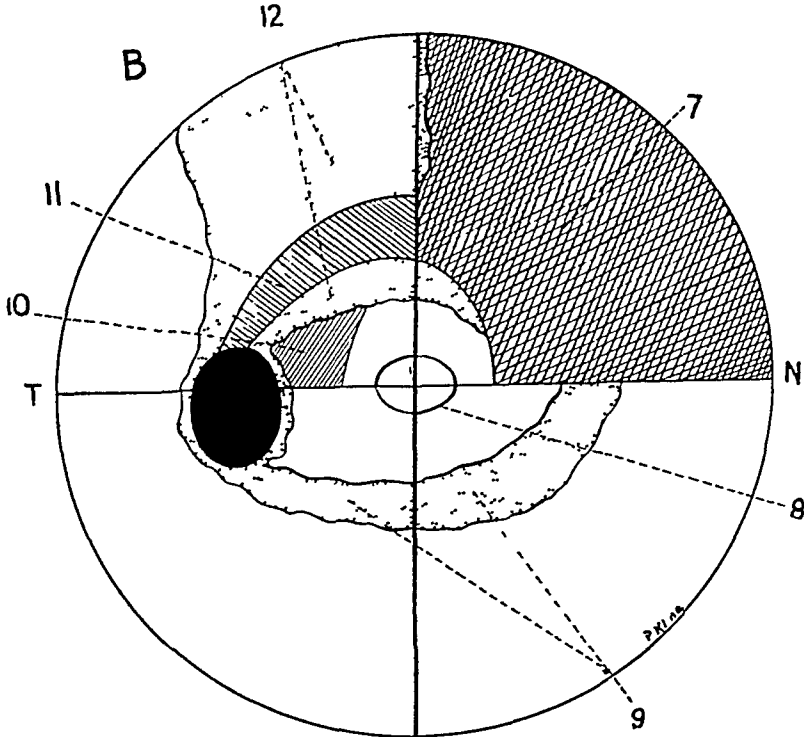
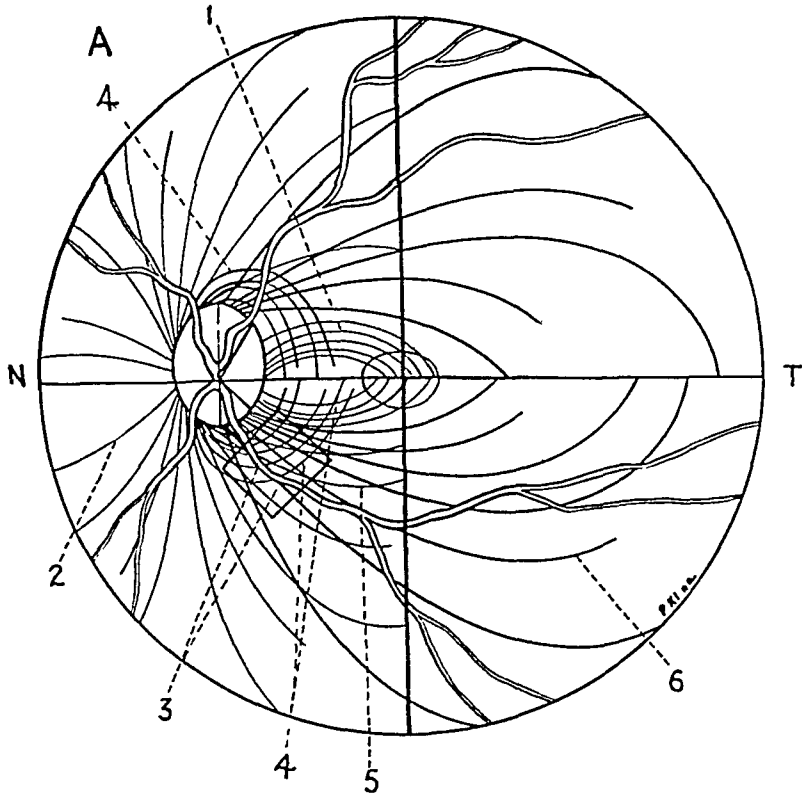
Figure 1A is a schematic representation of our concept of the relation of nerve fibers to one another and to the vascular tree. From the diagram, it is readily seen that the papillomacular bundle occupies two thirds or more of the temporal half of the optic nerve. All the fibers derived from the temporal half of the retina (nasal field) are crowded into the remaining upper and lower sixths of the temporal half of the nerve. The fibers coming from the nasal half of the retina (temporal field) occupy the nasal half of the optic disk.

In lesions of the optic pathways, the dividing line between the nasal and the temporal field is a vertical line drawn through the fixation point. We believe with Evans<sup>2</sup> that the vertical line through the macula divides the temporal from the nasal portion of retina. We have, therefore, drawn

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1 Part of the material used in this study was taken from the files of the late Dr. Mark J. Schoenberg.

2 Evans, J. N. Classic Characteristics of Defects of the Visual Field, *Arch Ophth* 22:410-431 (Sept.) 1939.



all the fibers which supply the peripheral portion of the retina nasal to the vertical meridian as belonging to the nasal half of the nerve. In this respect, our diagram is at variance with those generally found in textbooks, in which the area included between the macula and the optic disk is not accounted for.

The foregoing assumption is supported to some extent by the work of Brouwer and Zeeman.<sup>3</sup> These authors made an incision in the lower part of the retina between the macula and the optic disk. They found some degeneration in the area of the crossed peripheral fibers in the optic tract and the external geniculate body. Traquair<sup>4</sup> admitted that the segregation of crossed and uncrossed fibers into separate bundles holds true in the optic nerve even "immediately behind the eye," and he assumed that this "would necessitate a rearrangement of fibers between the retina and the beginning of the nerve." We know of no anatomic proof of this rearrangement. We thus feel justified in assuming that the area of the retina included between the vertical meridians passing through the fovea and the optic disk, respectively, is nasal retina. The nerve fibers derived from this area enter the nasal half of the nerve.

The relation of the circulation to glaucoma has been stressed by numerous authorities. More recently, Reese and McGavie<sup>5</sup> have demonstrated that a connection exists between the blood pressure and the changes in the fields in cases of glaucoma. Evans<sup>6</sup> described capillary aneurysms associated with glaucoma, which may be related to a derangement in the capillary sphincter mechanism. Although the entire retina is probably affected by glaucoma, the areas of greatest vulnerability appear

3 Brouwer, B., and Zeeman, W. P. C. Projection of Retina in Primary Optic Neuron in Monkeys, *Brain* **49** 1-35 (March) 1926

4 Traquair, H. M. Introduction to Clinical Perimetry, ed. 5, London, Henry Kimpton, 1946, p. 75

5 Reese, A. B., and McGavie, J. Relation of Field Contraction to Blood Pressure in Chronic Primary Glaucoma, *Arch. Ophth.* **27** 845-850 (May) 1942

6 Evans, J. N. The Capillary Sphincter in the Human Retina, *Arch. Ophth.* **37** 182-188 (Feb.) 1947

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Fig. 1—Schematic representation of the evolution of defects in the visual fields associated with glaucoma. *A* indicates arrangement of nerve fibers and blood vessels in the retina, *B* shows a typical visual field in glaucoma. 1 is papillomacular bundle, 2, nasal fan, 3, area of greatest nutritional disturbance, 4, nasal fibers to area between disk and macula, 5, nasal fibers, 6, temporal fibers, 7, defect in upper nasal field, showing nasal step, 8, fixation area, 9, lower arcuate scotoma, 10, juxtacecal step, 11, upper arcuate scotoma, 12, intermediate zone between arcuate scotoma and nasal defect.

The area of maximum circulatory disturbance (3) corresponds in part to the arcuate scotoma (11). Nasal and temporal fibers passing through this area may become involved, resulting in the juxtacecal step (10) and nasal defects (7), respectively. Intermediate zone (12) is partly neural and partly circulatory in origin.

to be in the proximity of the superior and inferior temporal branches of the central retinal vessels. This may be accounted for by the great crowding of nerve fibers in this region. All the temporal fibers, in addition to many nasal fibers, of necessity pass through this narrow zone (fig 1A, 3). It is possible that the perimacular area drains, partially at least, into this region of the retina, thus increasing still further the strain on the circulation. The area around the inferior temporal vessels appears to be more vulnerable than that adjoining the superior temporal vessels, for reasons which will be given later.

Figure 1B shows schematically the changes in the fields associated with glaucoma. The earliest change is an accentuation of the angioscotoma tree.<sup>7</sup> These scotomas are first reversible, or at any rate show fluctuations on repeated examinations. Later, however, the permanent arcuate scotoma is formed. This probably represents local damage to the cellular and synaptic structures of the internal layers of the retina. It is reasonable to assume that the nerve fibers passing through this area are also eventually affected. Interruption of the nerve fibers is manifested by a field defect at an area remote from the point of involvement and corresponds to the distribution of the end organs of these fibers. If a few scattered fibers are thus affected, there will result a depression of the upper nasal field to the smallest stimulus. As more fibers become involved, the defect takes on the appearance of a nasal step. The latter, when developed, ends with a steep slope (in the sense of Traquair's terminology) along the horizontal meridian, in contrast with the arcuate scotoma, which is characterized by a more gradual slope. We shall attempt to show in the field studies to follow that, generally speaking, a steep slope indicates a neural origin, whereas a gradual slope denotes that the scotoma is chiefly of circulatory origin.

Although the majority of nerve fibers which pass through the area of greatest vulnerability come from the temporal portion of the retina, a certain number of nasal nerve fibers also transverse this region. Among the latter are fibers which supply the area between the disk and the macula (fig 1A, 4). Judging from the low visual acuity of this region, these fibers are probably few. Since they supply the retina beneath the papillomacular bundle, it is easily understood that they may not be detected by red-free ophthalmoscopic examination, by which the more superficial layers are visualized. Involvement of these fibers produces a scotoma such as that in figure 1B, 10. This defect is frequently found in the fields in cases of glaucoma, and examples will be shown later. A similar configuration in various stages of development was noted in

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7 Evans, J. N. *An Introduction to Clinical Scotometry*, New Haven, Conn., Yale University Press, 1938, p. 104.

studies of the visual fields reported by several authorities<sup>8</sup> These authors did not differentiate this area from the rest of the arcuate scotoma and apparently regarded it as an integral part of the latter The neural origin of this scotoma is evidenced by the fact that it ends abruptly at the horizontal meridian, in this respect, it is analogous to the nasal step of Ronne For the sake of brevity, this scotoma will be referred to as the juxtacecal step

#### DEVELOPMENT OF THE ARCUATE SCOTOMA

In glaucoma, the earliest changes detected in the region corresponding to the arcuate scotoma consist in widening and accentuation of the angioscotomas Figure 2*A*, right eye, is the field of a patient with recurrent glaucomatocyclitic crises in that eye<sup>9</sup> The angioscotomas widened during the attack but became normal after subsidence of the ocular hypertension The left eye was amblyopic

*B* and *C* of figure 2 show fields from cases of early glaucoma Repeated examinations showed persistent widening of the angioscotoma tree, although the pattern varied from time to time

Figure 3*A*, right eye, shows a more advanced stage, with a permanent widening of the upper angioscotoma The left eye shows the end result of this process, consisting in a merging of the angioscotoma with the corresponding nasal field defect to form a nasal step

Figure 3*B*, left eye, shows the arcuate defect in a shape characteristic of Bjerrum's scotoma It arches upward and nasally above the fixation area to end in the horizontal meridian It is permanent, having remained unchanged for several years The terminal segment of this scotoma has a steep slope and is probably caused by damage to the nerve fibers which pass through the region of impaired circulation in the retina The proximal segment has a gradual slope and is chiefly of circulatory origin

Figure 3*C*, right eye, shows a relatively dense defect in the nasal field, from which a tongue-shaped projection extends toward the upper angioscotoma This scotoma is reminiscent of the description of the formation of the arcuate scotoma, as given by Traquair,<sup>10</sup> namely, that it begins at some distance from the blindspot and extends toward it It is seen from

<sup>8</sup> van der Hoeve, J Visual Field Defects and Operative Procedures in Glaucoma [table 9, fig 11], *Ztschr f Augenh* 34 277-289, 1915 Traquair,<sup>4</sup> p 126, fig 71*B*, 73*A* (left eye), fig 78*A* (right eye) Elliot, R H A Treatise on Glaucoma, ed 2, New York, Paul B Hoeber, 1922, p 251, fig 64 (right eye) and fig 65 (left eye) Bjerrum, J An Additional Method of Visual Field Measurements and the Visual Field in Glaucoma [fig 16], *Verhandl d Internat M Cong* 4 78, 1890

<sup>9</sup> Posner, A, and Schlossman, A A Syndrome of Recurrent Attacks of Unilateral Glaucoma with Cyclitis Symptoms, *Arch Ophth* 39 517 (April) 1948

<sup>10</sup> Traquair,<sup>4</sup> p 134



the figure that the entire area which corresponds to the upper angioscotoma tree is functionally depressed, but that this depression is most pronounced in two zones. The one near the blindspot corresponds to the

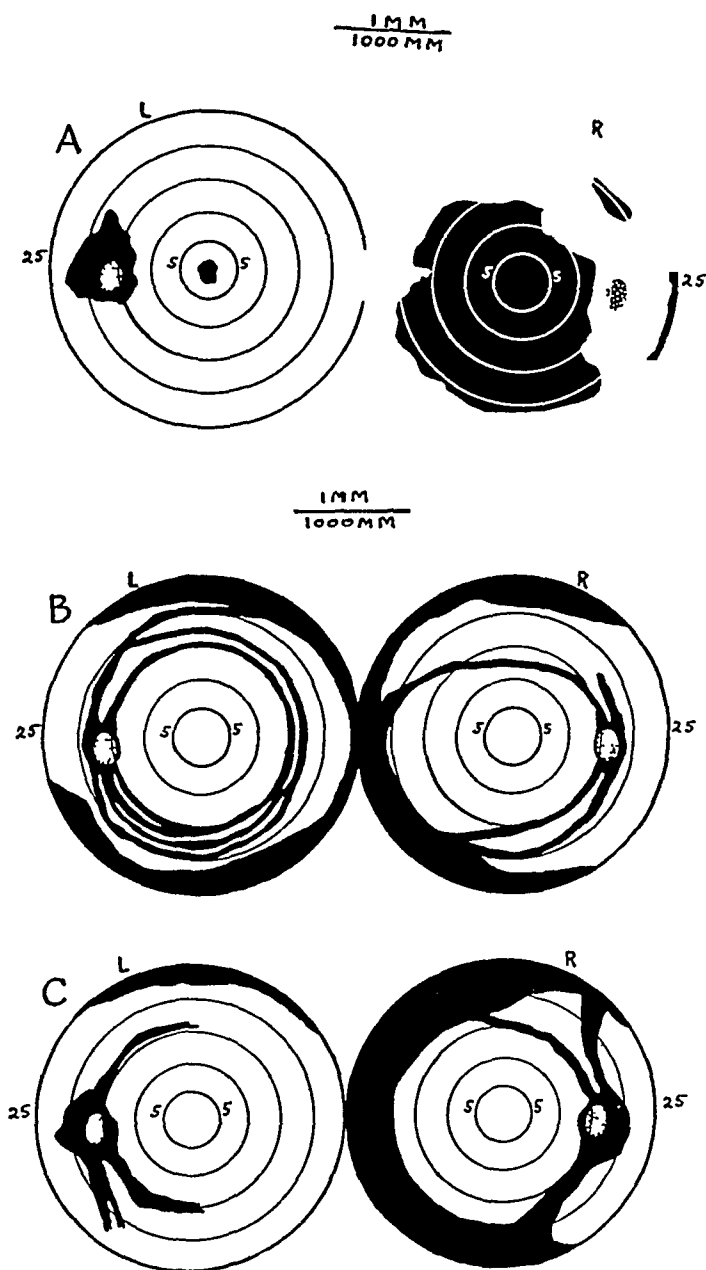


Fig 2—(A) Right eye widened angioscotomas, which are reversible (recurrent glaucomatocyclitic crises in the right eye (B and C) Widened angioscotomas, variable pattern, in a case of early glaucoma

greatest circulatory disturbance, the zone extending from the nasal defect has a neural element added to the circulatory element common to the entire area

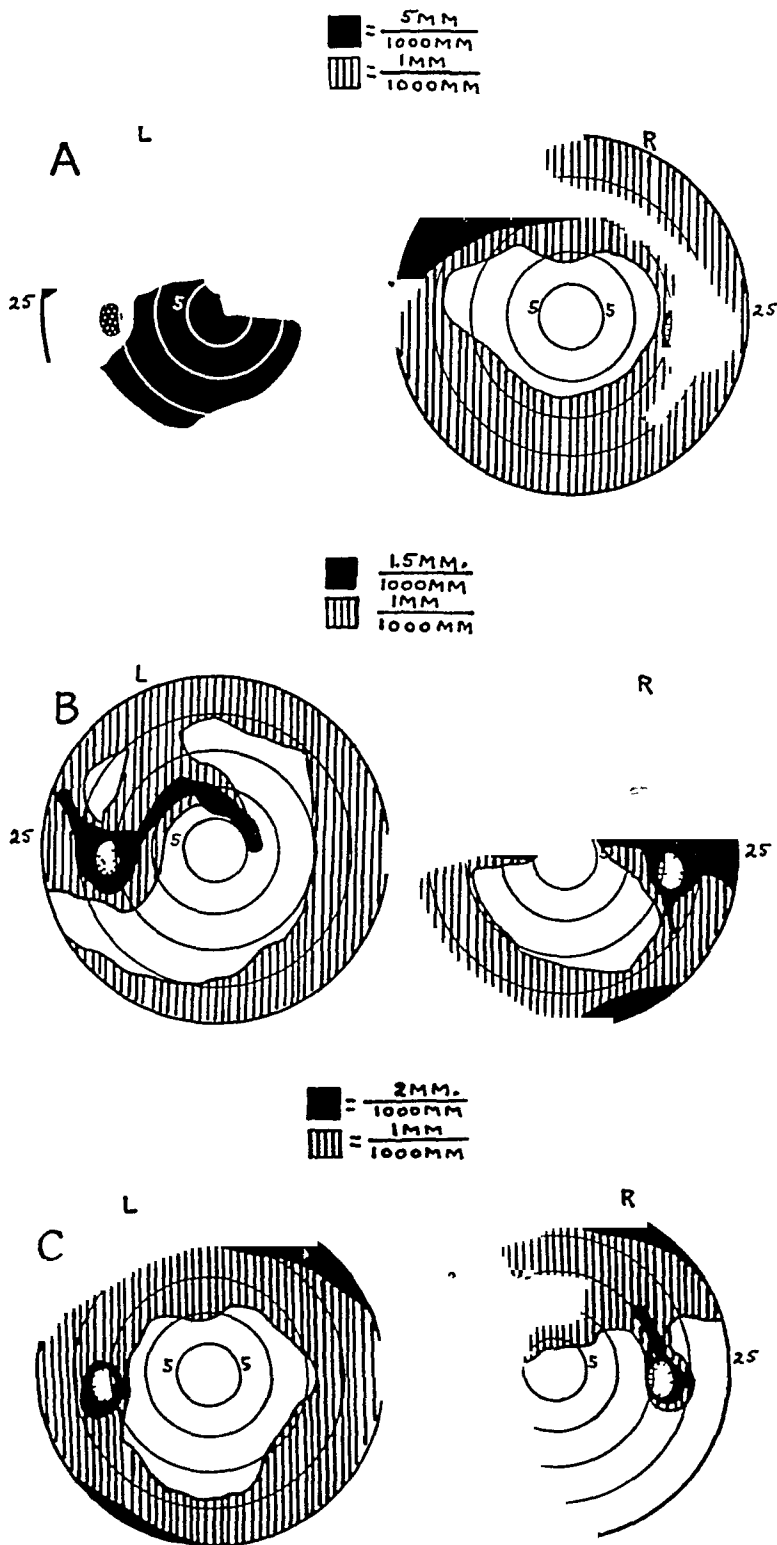


Fig 3—(A) Right eye early arcuate scotoma, permanent, left eye upper nasal defect merging with arcuate scotoma (B) Right eye early upper horizontal hemianopsia, left eye arcuate scotoma with nasal step (C) Right eye nasal defect with incomplete arcuate scotoma of circulatory and neural origin, left eye moderate generalized contraction

The field of the right eye shown in figure 4A may be explained by assuming that a bundle of nerve fibers belonging to the nasal portion of the retina is damaged as it crosses the area of maximally impaired nutrition. This is substantiated by the fact that the arcuate scotoma stops abruptly at the vertical meridian. The dividing line between the circulatory and the neural elements of this scotoma is probably at *a*.

Figure 4B, left eye, illustrates the relation of the arcuate scotoma to the defect in the nasal field. The latter ends in a line which corresponds

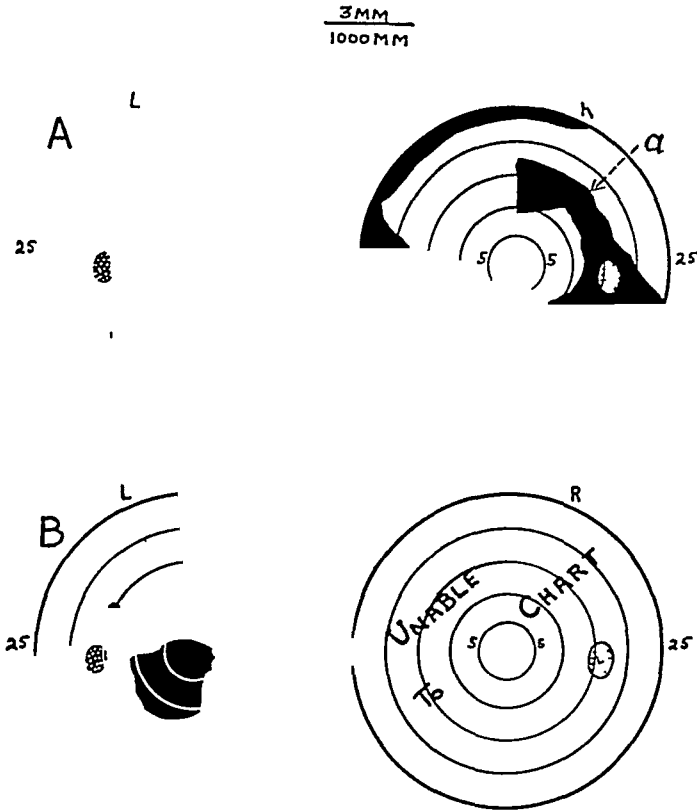


Fig 4—(A) Right eye upper arcuate scotoma, ending in vertical meridian, at division between neural and circulatory elements, left eye blindness (B) Left eye upper arcuate scotoma with juxtacecal step, connecting with area of nasal hemianopsia

to the vertical meridian passing through the fixation point, and is thus probably neurogenic. The lower border of the upper arcuate scotoma extends in a straight line along the horizontal meridian as far as 6 degrees from the fixation point. This represents the juxtacecal step.

These eight field studies demonstrate that the arcuate scotoma is composed of neural and circulatory elements, which may be combined in a varying quantitative relation to each other. The involvement of nasal fibers is demonstrated by the juxtacecal step (fig 4B) and by the abrupt ending of the arcuate scotoma at the vertical meridian (fig 4A). In-

involvement of the temporal fibers is shown by the nasal step. It will be seen that when two sizes of test objects were used scotomas of the circulatory origin had a more gradual slope than the neurogenic scotomas.

#### DEVELOPMENT OF THE NASAL FIELD DEFECT

The arcuate scotoma is described as typically ending in the horizontal meridian in a nasal step. A defect involving both the upper and the lower nasal quadrant is assumed to be produced by a combination of two

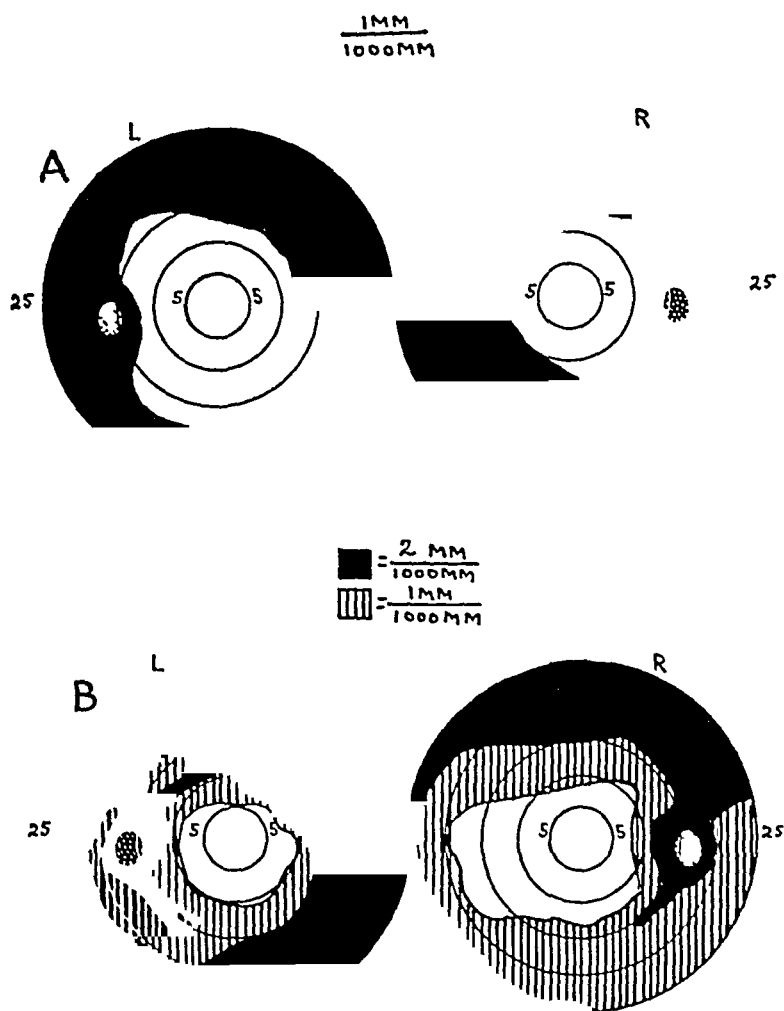


Fig 5—(A) Early irregular nasal contraction (B) Right eye early generalized contraction, left eye generalized contraction, predominantly nasal

nasal steps. Analysis of many field studies shows that a typical nasal step is by no means a constant finding but that defects in the nasal field may take on various shapes. A few examples are shown in figures 5 to 8.

Figure 5 A shows the irregular indentation of the nasal field to a 1 mm test object in a case of early glaucoma. This change may be partly an expression of the generalized lowering of retinal function, which is more pronounced in the nasal field as a result of impairment of a few

scattered temporal fibers as they cross the zone of maximum nutritional disturbance in the retina. Figure 5 *B*, left eye, shows a similar field, but with more advanced changes.

Figure 6 *A*, left eye, shows two types of early defects in the nasal field. The lower is caused primarily by a confluence of angioscotomas, while the upper exhibits an early nasal step which is probably neural and is not connected with the corresponding angioscotoma. Figure 6 *B*, right eye,

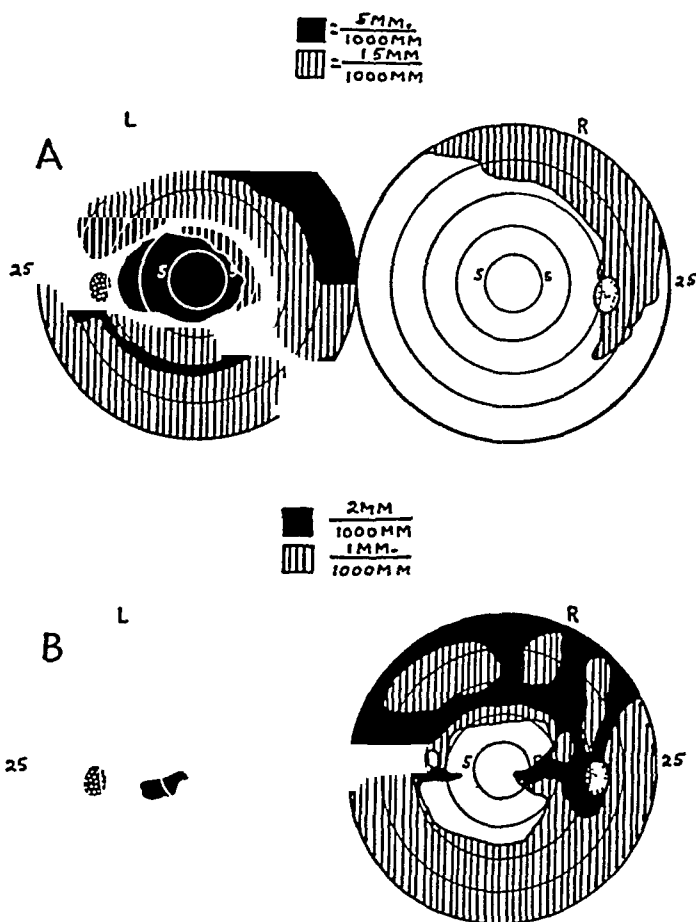


Fig 6—(A) Right eye normal, left eye early upper nasal step (neurogenic), lower nasal defect (of circulatory origin). (B) Right eye: upper nasal step, probably of circulatory origin, connected with widened angioscotomas, left eye late contraction of field

demonstrates clearly how the confluence of angioscotomas may produce a nasal step and thus simulate a nerve fiber bundle defect. This may be explained by the presence of a vascular raphe in the horizontal meridian.

Figure 7 *A* shows bilateral defects in the nasal field in later stages of development. The right field shows, in addition to the nasal step, generalized contraction to a 1 mm test object. The left eye, at first glance, appears to show a typical nasal step. However, on careful analysis, it will

be noted that the lower border does not extend to the horizontal meridian passing through the fixation point, but is situated 4 degrees above.

Figure 7 *B*, left eye, demonstrates a typical defect in the upper nasal quadrant, which ends at a steep slope in the horizontal meridian. This is connected with the blindspot by two arcuate scotomas, which lie in an area of depressed retinal function.

Figure 8 *A*, left eye, is a similar field, but without a pronounced arcuate defect. Figure 8 *B*, right eye, shows in addition to a nasal de-

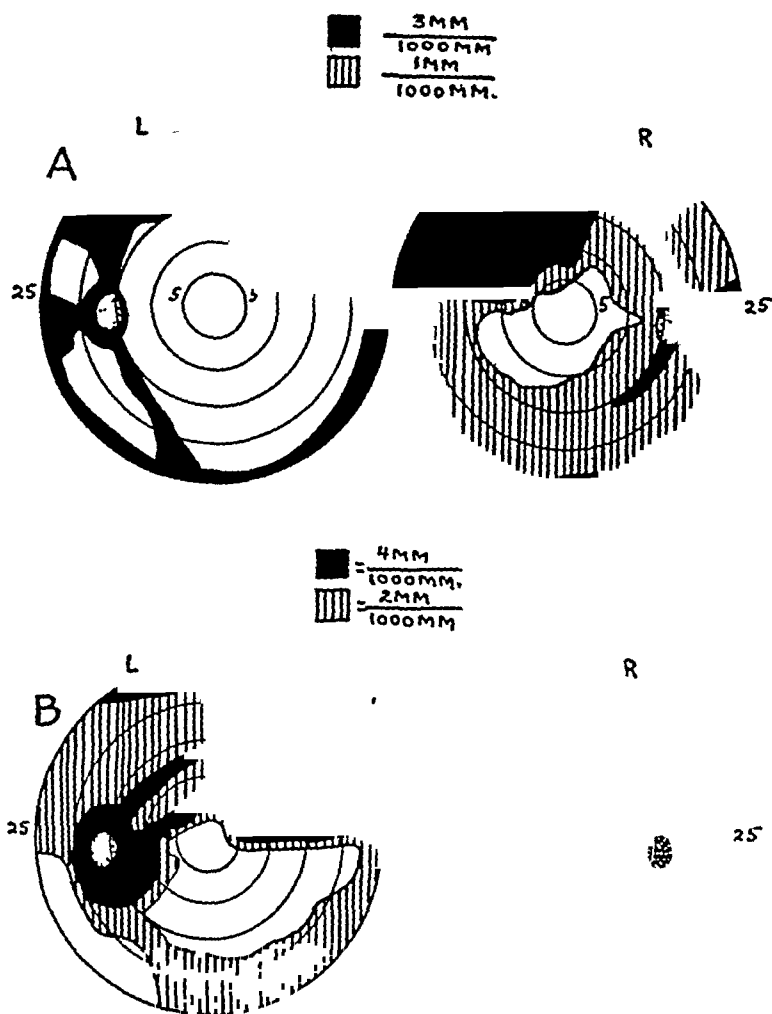


Fig 7 —(A) Bilateral upper nasal defects (B) Right eye blindness, left eye defect of upper nasal quadrant (neurogenic), connecting with arcuate scotoma

fect, moderate encroachment on the upper half of the fixation area and a juxtacecal step which extends from the arcuate scotoma to the horizontal meridian. Figure 8 *C* shows a nasal step in the right eye and loss of both nasal quadrants in the left eye. The latter also demonstrates the juxtacecal step.

Like the arcuate scotoma, the defect in the nasal field contains both circulatory and neural elements. The nasal step is the result of involve-

ment of nerve fibers as they cross the area of maximal circulatory disturbance of the retina. Figure 1 shows why the defect in the nasal quadrant, when present, generally occurs on the side of the more advanced arcuate scotoma.

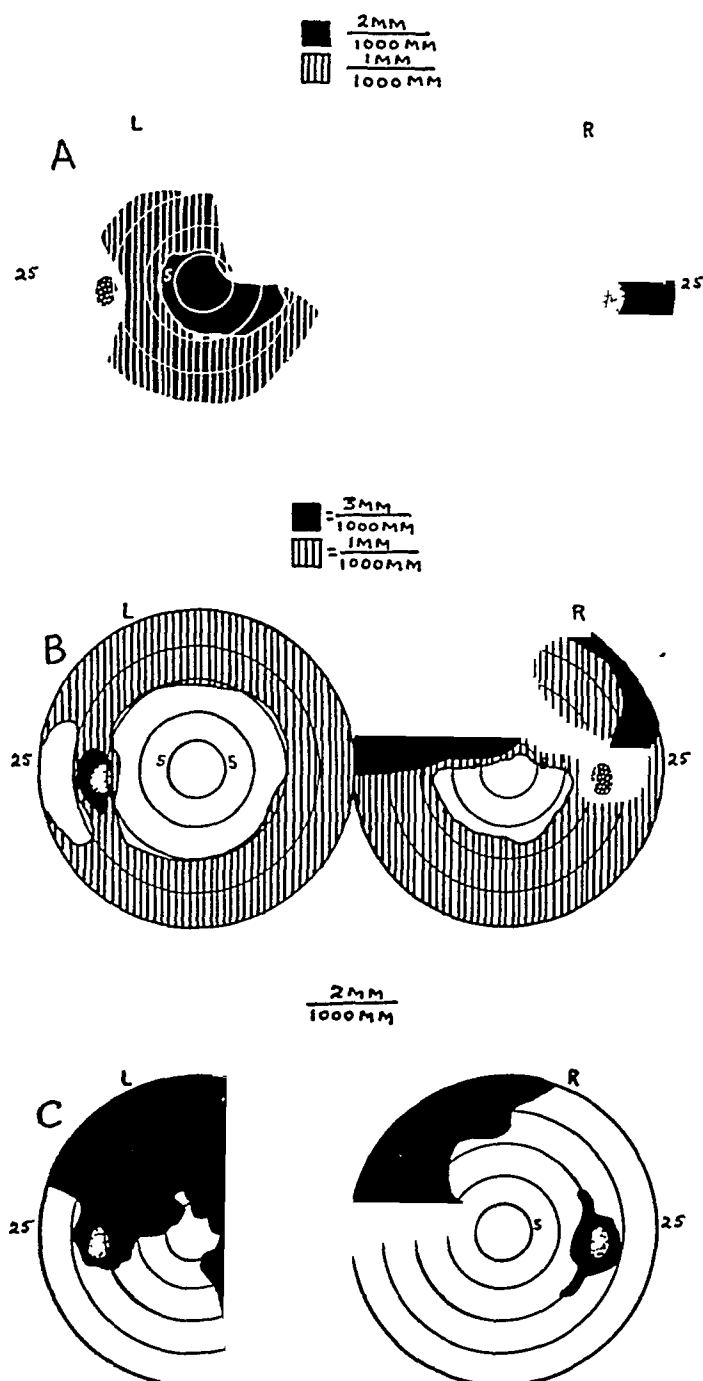


Fig 8 — (A) Right eye blindness, left eye defect of upper nasal quadrant (B) Right eye defect of upper nasal quadrant, with arcuate scotoma and juxta-ecal step, left eye mild generalized contraction (C) Right eye defect of upper nasal quadrant with nasal step, left eye nasal contraction, predominantly of upper quadrant, connecting with blindspot and juxta-ecal step

## OTHER FIELD DEFECTS

While the arcuate scotoma and the defect in the nasal field belong to the classic picture of the field associated with glaucoma, other types of defects are occasionally encountered. In 3 cases the temporal field alone was affected. In 1 of these cases this defect was related to widening of the lower temporal angioscotoma. In several cases a more or less generalized contraction of the field was an early sign, but here the contraction often appeared to be more advanced in the nasal field (fig 5).

In the majority of cases the fixation area is spared until late. However, early involvement of this region is not unusual. This may occur either as the result of extensions from the angioscotomas or through direct damage of some of the fibers of the papillomacular bundle which pass in close proximity to the area of greatest nutritional disturbance in the retina. The rectangle in figure 1*A* was drawn to include some of the papillomacular fibers in order to demonstrate how such partial involvement of the fixation area may come about.

## TECHNIC USED IN THIS STUDY

The initial study of the field in each case was made on the perimeter and the tangent screen. Subsequent examinations were carried out at varying intervals, more frequently on the tangent screen. The perimeter used was a nonrecording instrument, with a radius of 250 mm and a built-in illuminating unit giving an illumination of  $7\frac{1}{2}$  foot candles.

The tangent screen was 1 meter square, covered with black wool felt and placed 1 meter from the patient. For most of these field studies, illumination was provided by an over-head light which, aided by reflection from a light-colored wall behind, yielded a uniform illumination of 5 to 6 foot candles. For the past ten years, small white spherical test objects, as devised by Evans, were used. They were supplemented by the Berens test objects when sizes larger than 1.5 mm were necessary.

In addition to the conventional methods of scotometry, the Evans technic of angioscotometry<sup>11</sup> was adapted for use with the tangent screen.

## COMMENT

Although the defects in the visual fields associated with glaucoma may assume a wide variety of patterns, they can be broken up into component units which are more or less characteristic of the disease, namely, early widening of the angioscotomas, generalized contraction to small test objects, the arcuate scotoma of Bjerrum, nasal field defects, the nasal step of Ronne and the juxtacecal step. These component parts show a varying

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<sup>11</sup> Evans,<sup>†</sup> p 61



degree of circulatory and neural elements in their pathogenesis. The relative preponderance of one or the other of these elements may be estimated by the slope of the border of the scotoma and by its relation to the distribution of nerve fibers and blood vessels in the retina (fig 1*A* and *B*). Our concept of the pathogenesis of the field defects associated with glaucoma was outlined in an earlier section of this paper. Two of the more commonly accepted alternative theories are (1) damage to nerve fibers at the margin of the glaucomatous cup, and (2) traction on the nerve fibers, resulting from the receding lamina cribrosa.

It is inconceivable how hydrostatic pressure can push the nerve fibers against the optic cup, since the nerve fibers do not form a membrane impervious to water. On the contrary, they are permeated by intraocular fluid, and hence the hydrostatic pressure around them must necessarily be the same. The physical factors involved in the formation of glaucomatous cupping are different from those affecting the nerve fibers within the eyeball. In the first case, the pressure behind the lamina cribrosa is less than the intraocular pressure, but within the eyeball the hydrostatic pressure is approximately the same throughout. In fact, Traquair<sup>12</sup> stated

the frequently advanced explanation of the production of field defects in glaucoma by compression of the nerve fibers against the edge of the scleral foramen cannot be regarded as satisfactory.

Stretching of the nerve fibers by the receding lamina cribrosa may be a factor, but is certainly not an important one. The visual field is not as a rule related to the amount of cupping, though in a few cases it is related to the site of the greater pallor. Furthermore, it is evident from the histologic sections of glaucomatous eyes that, even in deep cups, the nerve fibers are not stretched between the edge and the floor of the cup (like fiddle strings) but follow the contour of the excavation.

In only 3 of 400 cases was there early involvement of the field temporal to the blindspot. The reason for the preponderance of nasal defects is not definitely known. Two factors are suggested as a partial explanation. The majority of nerve fibers which pass through that part of the retina which corresponds to the arcuate scotoma go to the temporal portion of the retina, and their involvement causes a defect in the nasal field. Moreover, reference to figure 1*A* demonstrates the extreme crowding in the region in question. For this reason, the nerve fibers passing through this area would be more vulnerable to circulatory or metabolic dysfunction.

The upper nasal quadrant is more often affected than the lower. Again, carrying this concept a little farther, it will be seen from figure 1*A* that there is relatively more crowding of those fibers which emerge

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12 Traquair,<sup>4</sup> p 135

from the lower temporal quadrant of the disk than of those arising from the upper temporal quadrant. This is because the horizontal raphe, which passes through the fovea, intersects the optic disk about 15 degrees below its geometric center. This difference is significant when one realizes that the vertical diameter of the disk is only about 7 degrees. Additional evidence may be adduced from analysis of the cecocentral scotoma in cases of tobacco amblyopia, strabismus and other conditions.

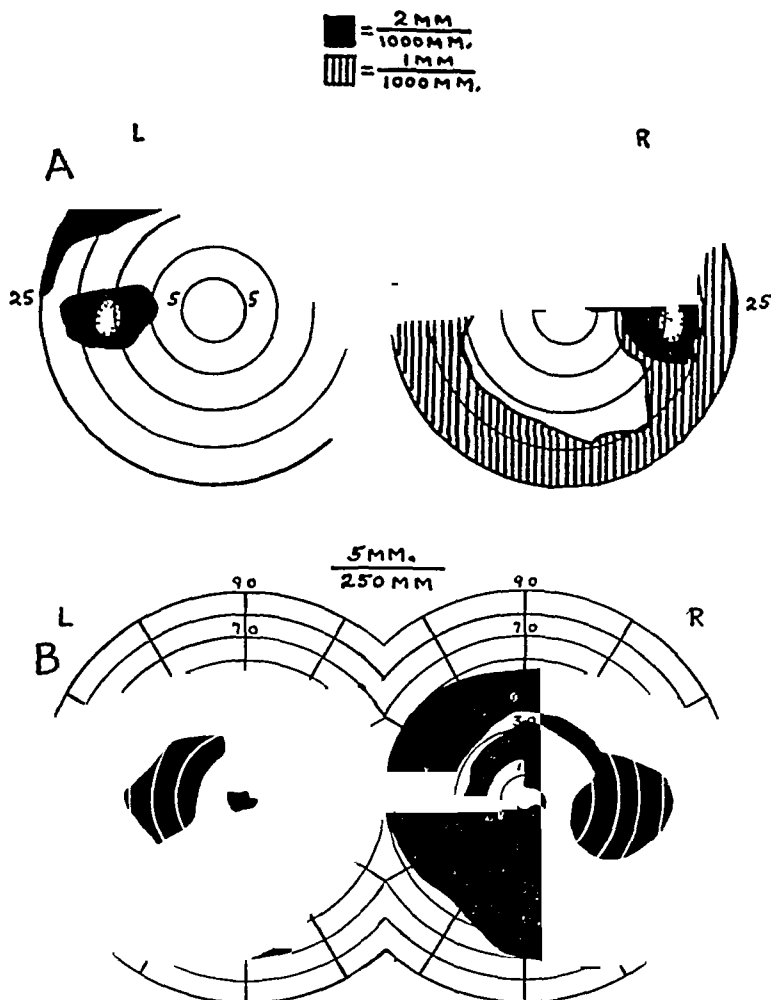


Fig 9—(A) Right eye upper horizontal hemianopsia and moderate enlargement of the blindspot, left eye upper nasal contraction and moderate enlargement of the blindspot (B) Field in a case of late glaucoma, showing preservation of small central and temporal islands

In the majority of such cases, the cecocentral scotoma extends from the fixation point in a horizontal direction and meets the blindspot above its geometric center. This, again, indicates that the functional division between the upper and lower halves of the optic disk is not identical with the geometric center, but lies below it and is on a level with the horizontal raphe.

Where both nasal quadrants are involved to give the appearance of a nasal hemianopsia, it is not necessary to assume that two nasal steps have joined. A more or less generalized contraction of the field, especially the nasal half, is characteristic of glaucoma. This may be due to a diffuse involvement of nerve fibers originating in the temporal half of the optic nerve. This view is corroborated by fields showing defects of the nasal quadrant which are not delimited by the horizontal raphe. The circulatory elements may also play a role in the formation of this type of defect.

The formation of horizontal hemianopsia (fig 9A) in glaucoma may be interpreted as a fusion of three components, namely, the arcuate scotoma, the juxtacecal step and the nasal step. Encroachment on the fixation area may be due to direct involvement of the papillomacular bundle, or it may be of circulatory origin and related to the arcuate scotoma. The horizontal hemianopsia found in the closure of a temporal branch of the central retinal artery may originate in a manner similar to that just described.

It is well known that the fixation area is usually spared until late in the course of the disease. The reason for this is not definitely known. Figure 1A points to a possible explanation of this peculiarity. A large part of the papillomacular bundle passes from the disk directly to the macula without passing through the region of maximally impaired retinal nutrition. Furthermore, the macular area has its own source of blood supply both from the choroid and from the retina, by way of the macular branches.

Usually, the last part of the field to be destroyed is a small island in the temporal periphery (fig 9B). The reason for the preservation of this portion of the field may be deduced by referring to the diagram in figure 1A. This area corresponds to the peripheral nasal portion of the retina, which is characterized by the least crowding of nerve fibers and is relatively avascular. Moreover, the fibers supplying this area do not pass through the zone of greatest retinal vulnerability. In this sense, the nasal periphery of the retina may be compared to the macular area.

The variability of field defects in patients with glaucoma is probably dependent not only on the pathologic process but also on the anatomic relation of the nerve fibers to the circulation.

The value of understanding the mechanism of the evolution of the field associated with glaucoma is not purely academic. In many cases, it enables one to predict the probable direction which future changes in the fields will take. It emphasizes the importance of the role played by the progressive arcuate scotoma in determining the pattern of peripheral loss of field. This phase will be the subject of a future communication.

## SUMMARY

Approximately 2,000 visual fields in 350 cases of primary glaucoma were studied and classified

The development of the characteristic field changes was analyzed by breaking down these defects into their component units, namely, the arcuate scotoma, the nasal field defect and what we term the juxtacecal step

It is shown that a relationship exists between the circulatory and the neural elements of the glaucomatous field and that most defects result from a mixture of these two components in varying quantitative combinations

The concept outlined in this paper has prognostic value

667 Madison Avenue

# ENTROPION IN INFANCY CAUSED BY FOLDING OF THE TARSUS

## Report of a Case

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### REPORT OF CASE

An infant, born on Dec 22, 1946, was brought to the clinic on Jan 28, 1947. The mother stated that the child's eyes became inflamed on the third day after birth. She treated the eyes with camomile compresses, and the right eye recovered promptly, whereas the left eye remained closed and the discharge continued.

Examination showed that the right eye was normal except for redness of the conjunctiva and slight roughness above the convex tarsal margin.

The margin of the lid of the left eye was fully turned, resembling the picture of spastic entropion. The conjunctiva was diffusely reddened, with a smooth surface. In the center of the cornea there was a deep, round, sharp-edged infiltration, 3 mm in diameter and of torpid character. The whole corneal surface showed a superficial haziness. Bacteriologic examination revealed no pathogenic organisms.

The entropion was unusual. Spastic entropion does not occur in the first weeks of life. There is a well known congenital form of turning in of either or both lids, caused by the so-called epiblepharon, in which the possibility of muscular overaction may be a secondary factor, but in this form the entropion remains partial, and the eyelashes only are turned in, not the whole lid.

The real nature of the entropion came to light when the lid was everted, which was done with difficulty. An edematous, bulging cul-de-sac appeared, exposing a tarsus fully folded in a horizontal direction. When the lid was replaced in its previous position, the anatomic cause of the inversion was easily evident, the tarsus, being the skeleton of the lid, was folded like two closed leaves of a book (fig 1). The line of folding ran along the horizontal middle line of the tarsus. There was no pathologic change in the tarsal surface, not even a whitish or reddened line, the tarsus looked as though it might have been freshly twisted between the fingers.

By pressing on the skin of the lid with the finger against a lid plate, one could smooth out the tarsus. The result, however, did not last, and in a few minutes the tarsus curved in again and the entropion reappeared.

Obviously, some force had folded the sound tarsus and had kept it in that position for weeks. It had become accustomed to its new form, and a short period of straightening could not correct the deformity. This explanation suggested the operative solution of the problem. The tarsus must be kept in redressed position for a few days, this should be accomplished without deeper intervention.

A lid plate was introduced into the upper cul-de-sac, with pressure against the lid, and the tarsus was thus smoothed out. Then a gauze roll, 4 mm in

thickness, was placed on the lid above its margin and fixed with two knotted mattress sutures (fig 2 *A*). The sutures were inserted on both sides of the roll, deep enough to take up the tarsal tissue. Thus, the tarsus was kept in a straightened position until the sutures were removed (fig 2 *B*).

Five days later the sutures and the roll were removed. This period was sufficient to reaccustom the tarsus to its normal, straightened position. The entropion

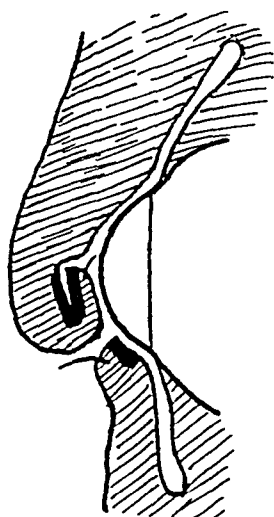


Fig 1—Cross section of the entropion

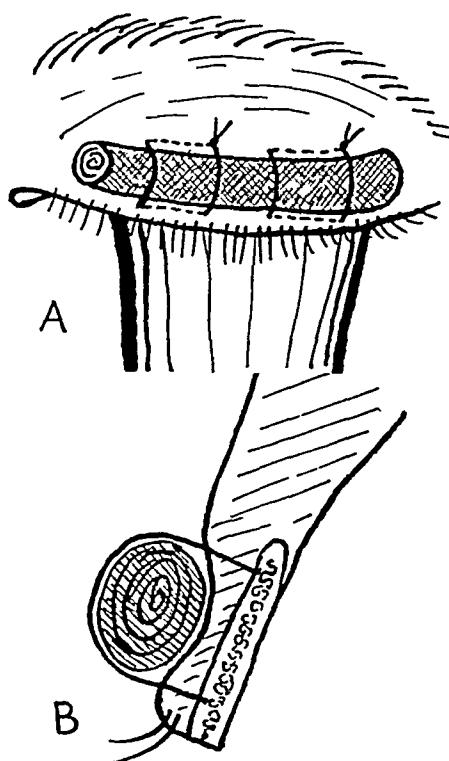


Fig 2—*A*, operative correction of the tarsus by two mattress sutures, *B*, cross section of the operation

disappeared, and the cornea cleared up except for the central infiltration, which developed into a macula

If this solution had not proved correct, and if the entropion had reappeared, I had planned to perform Kuhnt's tarsectomy, removing the upper broken part of the tarsus

I believe that the inversion was produced as follows. The severe inflammation caused infiltration and edema of the upper fornix. The bulging conjunctiva hung down as a relatively heavy weight on the convex tarsal margin (fig 3 *A*). The levator muscle was temporarily paralyzed, and the tarsus, still soft and tender in the newborn infant, became folded. The fold, having existed for a few weeks, became fixed. When the edema disappeared and the levator muscle regained its power, the convex tarsal margin was drawn back into its original place, but the fold, being fixed, turned the margin of the lid inward (fig 3 *B*). Restoration did not seem possible without surgical aid.

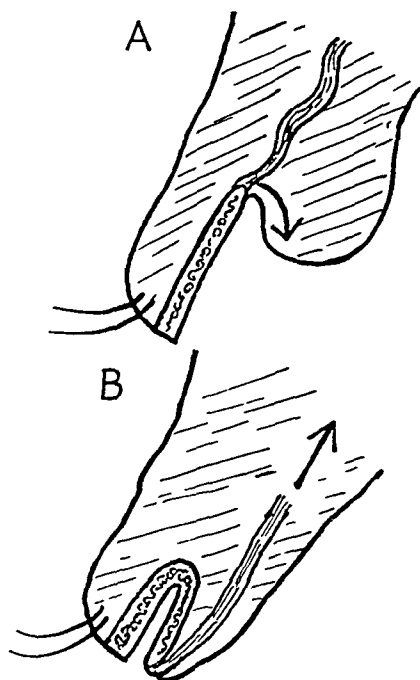


Fig 3—Explanation of the cause of the entropion, showing (*A*) breaking down of the tarsus and (*B*) regained tension of the levator muscle, which causes the folded tarsus to turn inward.

#### COMMENT

This strange form of entropion in infancy has apparently not been mentioned in the literature. Perhaps it is not so rare as it would seem. I myself remember having seen a few cases of entropion after purulent ophthalmia in infants, and in 1 case I performed a modified Hotz operation on both sides. I now believe that an origin similar to that just described existed in those cases. The case reported here was the first in which all the features of the entropion were clearly apparent and in which a hint of the origin was given and a simple method of operative correction indicated.

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## BOXING INJURIES OF THE EYES

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EVIDENCE is on record to the effect that among major sports boxing occupies a special position, since it deliberately aims at producing head injuries<sup>1</sup> It has been pointed out that some of the more dramatic manifestations of these injuries are colloquially referred to by such terms as "knock-out," "grogginess" and "punch-drunk" and that, for this reason, it is not usually appreciated that such conditions indicate serious cerebral disorders It is true that similar injuries occur in sports other than boxing, e g, in football and wrestling, but here they are accidents, rather than sequelae of intentional acts

This paper presents clinical data suggesting that a statement similar to that referring to cerebral trauma may be made with regard to ocular injuries in boxing

### ILLUSTRATIVE CASES

CASE 1 —M L, aged 18, received a blow to the right eye during a boxing lesson at school Almost immediately, vision in this eye became blurred Ophthalmologic examination conducted on the same day revealed a hyphema filling two thirds of the anterior chamber The blood was absorbed within eight days, but the pupil was flattened in its upper part A peripheral tear in the iris, extending from 11 to 2 o'clock, was evident

CASE 2 —This case, of a youth aged 17, is essentially similar to case 1

CASE 3 —P E, aged 18, noticed that vision in his left eye was blurred after a boxing match Examination on the same day revealed visual acuity of 6/12 and small tears on the lateral edge of the left pupil, which was semidilated Gonioscopic examination (Goldmann) revealed a small, fresh area of cyclodialysis of traumatic origin, situated opposite 2 o'clock, in the angle of the anterior chamber During the subsequent fourteen days the tear closed gradually

CASE 4 —G G, aged 23, received a severe blow to his left eye while boxing He subsequently observed that the lower part of the visual field was blacked out Four weeks later a peripheral area of traumatic choroiditis of recent origin was

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From the Medical Research Committee, National Advisory Council for Physical Education

<sup>1</sup> Jokl, E The Medical Aspect of Boxing, Pretoria, Union of South Africa, J L van Schaik, Ltd, 1941



found in the upper part of the left fundus. Five months later the diagnosis of detachment of the retina, extending from 11 to 2 o'clock, was made. Two attempts at surgical treatment failed, and when he was last seen, a year after the boxing injury, a cataract was beginning to form.

CASE 5—P L, aged 30, was struck a severe blow on his left eye during a boxing match. Within a month the whole left retina became detached. An operation was performed in Switzerland, with unsatisfactory results. Two years after the injury the retina was still detached and lying in loose folds. No tear could be located.

CASE 6—P J, aged 16, was hit in the right eye during a boxing match. At an ophthalmologic examination fourteen days later, a vertical white area of retinal edema was seen. Three weeks later a choroidal tear was evident in the inferior temporal part of the fundus. Two years later the diagnosis of a flat, circumscribed retinal detachment was made. Surgical reposition was successfully carried out. The retina has since remained in position, for eighteen months.

CASES 7 and 8—Two additional cases of choroidal tear in boys aged 14 and 15 years, respectively, were essentially similar to the preceding cases. In both the tear was in the macular region, and visual acuities were as poor as 6/24 and 6/36, respectively. No retinal detachment appeared in the course of more than nine months.

CASE 9—J O'C, aged 39, a teacher, was demonstrating dodging in the boxing ring when his opponent hit him in the right eye. Within an hour he could not see with that eye. An extensive hemorrhage in the vitreous was observed, this cleared within a year, though at this stage visual acuity was still reduced to 6/18. Widespread macular changes were present. General examination revealed early arteriosclerosis and slight hypertension.

CASE 10—During a boxing bout, H R, aged 17, received a blow on the left eye, with the result that vision in this eye became blurred about an hour after he received the blow. At examination on the following day it was evident that he had unilateral keratoconus and that the blow had ruptured Descemet's membrane, with resultant edema and irritation of the eye. This condition lasted four weeks. The end result was slight scarring below the apex of the corneal cone.

#### SUMMARY

Ten cases of ocular injury due to blows incurred in "regulation" boxing are placed on record. Boxing occupies a special position among major sports in that it deliberately aims at producing head injuries.

New Standard Bank Building

## USE OF VASODILATORS IN SYPHILITIC ATROPHY OF THE OPTIC NERVES

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The causes of atrophy of the optic nerve are many and diverse. They include such unusual conditions as profuse hemorrhage and thallium poisoning, as well as more common causes, such as chronic glaucoma and cerebral tumor. In many cases the cause is a primary vascular lesion, angiospastic in nature, which occurs with acute retrobulbar neuritis, tobacco amblyopia and closure of the central retinal artery.

The present article will not be concerned with atrophy of the optic nerve due to any of the aforementioned factors, but will be limited to syphilitic atrophy of the optic nerve. It is possible for tobacco, or glaucoma, or a cerebral tumor to cause optic nerve atrophy in a patient who has syphilis. However, with the help of the history, the ophthalmologic examination, the neurologic examination, the Wassermann test, the roentgenogram of the skull and a study of the visual fields, it is usually possible to eliminate other causes of the atrophy and establish the diagnosis of syphilitic atrophy of the optic nerve.

The outlook for improvement, or even for maintenance, of vision in cases of syphilitic atrophy of the optic nerve is poor. In many cases the disease progresses to total blindness with or without the use of specific therapy. This is an instance in which knowledge of the causative factor (i.e., syphilis) or of the drug (i.e., arsenic) which is known to cure the disease is of little or no value in combating one of the most serious complications of the disease. This state of affairs recalls to mind Conklin's statement that first causes are like the vestal virgins—sacred but barren.

The various types of therapy recommended for syphilitic optic nerve atrophy are unphysiologic, to say the least. Gifford<sup>1</sup> mentioned spinal drainage with the intravenous injection of arsphenamine, the Swift-Ellis method (intraspinous injection of arsphenamized serum),

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Presented at the One Hundred and Forty-First Annual Meeting of the State of New York Section of Ophthalmology and Otolaryngology, May 8, 1947.

<sup>1</sup> Gifford, S. *Ocular Therapeutics*, ed. 3, Philadelphia, Lea & Febiger, 1942, pp. 334-339.

Suker's method of injection of mercury bichloride into the lateral ventricle, Gifford and Keegan's modification of Suker's method, in which the injection is made into the cisterna magna, and the production of hyperthermia with the use of injections of foreign protein, malarial inoculations, the fever cabinet or the injection of sulfur

Intensive therapy with certain arsenicals, such as sodium arsaniolate ("atoxyl") and tryparsamide, is contraindicated, according to some observers, because these drugs at times seem to induce the onset of optic nerve atrophy or to hasten its progress if it is already present

Many of the therapeutic procedures here mentioned are in the nature of blitzkrieg therapy, in which the body as a whole is subjected to sudden and violent physiologic changes. Fatalities are not unknown, and serious complications secondary to the treatment have been often reported

#### PATHOLOGY, PATHOGENESIS AND TREATMENT

Moore and Woods<sup>2</sup> mentioned that pathologic changes usually occur in the intracranial portion of the optic nerves distal to the chiasm. Degeneration occurs first in the marginal fibers of the nerves. There are thickening and perivascular round cell infiltration of the overlying membranes (especially the pia) and of the connective tissue septums of the nerve.

Among the theories of the pathogenesis of syphilitic atrophy of the optic nerve are the following:

- 1 The atrophy is due to the coexistence of syphilis and lymphogranuloma venereum. This theory has no foundation in fact.

- 2 The optic nerve atrophy depends on a nutritional disturbance of the optic nerve, due to syphilitic involvement of the blood vessels to the optic nerve. Abadie published several papers on this theory between 1924 and 1932. He expressed the belief that degeneration of the nerve fibers was due to an ischemia produced by spasm of the arterial walls, due either to syphilitic inflammatory tissue or to involvement of their sympathetic nerve supply. I shall return to this theory later, but I mention here that Moore and Woods asserted that this theory was ill founded.

- 3 The optic nerve atrophy depends on a disturbance of the normal relations of systemic blood pressure, retinal blood pressure and intraocular tension, with resultant disturbances in the nutrition of the optic nerve or retina.

Lauber and Sobanski have been the most ardent proponents of this theory. Their treatment consists in raising the general blood pressure by injections of epinephrine, ephedrine or atropine and in lowering the intraocular tension with pilocarpine, or by cyclodialysis in some cases.

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<sup>2</sup> Moore, J. E., and Woods, A. C. *Am J Ophth* 23:1 (Jan) 1940.

Sobanski<sup>3</sup> reported the results of this treatment in a series of 37 patients. Thirteen eyes were blind before treatment was started. After treatment, of the remaining 61 eyes, 40 showed improved vision, 11 no change and 10 deterioration of vision. Arruga<sup>4</sup> treated 15 patients by this method, only 3 had improved vision.

Moore and Woods stated the belief that this theory is unsupported by the observed facts.

4 The optic nerve atrophy depends on meningeal inflammation with the development of opticochiasmal arachnoiditis, which constricts the optic nerve or its blood supply. Moore and Woods expressed the belief that this theory may explain an occasional case.

5 The optic nerve atrophy is due to the combination of nutritional (vitamin) deficiency and neurosyphilis. Moore and Woods stated that this theory offers a fertile field for further experimentation.

In a later communication, Moore and Woods<sup>5</sup> discussed the results of the conventional forms of treatment of this condition. Finally, in a statistical analysis of 250 cases of treated syphilitic optic nerve atrophy, Moore, Woods, Hahn and Sloan<sup>6</sup> concluded that adequate treatment of early syphilis almost completely protects against the development of optic nerve atrophy and that of untreated patients with optic nerve atrophy, almost 65 per cent are blind within three years of the onset and nearly 90 per cent are blind after twelve years. Subdural therapy precipitated blindness in 10 per cent of the patients so treated. Of patients subjected to malarial therapy, only 18 per cent were blind after three years and no other cases of blindness occurred within fifteen years.

According to Lehrfeld and Gross,<sup>7</sup> the prognosis is poor in all cases of syphilitic atrophy of the optic nerve. They reported on 91 patients who were followed from five to eight years. These patients were divided into three groups.

The first group received no treatment for the optic nerve atrophy. All were blind, or nearly blind, on admission to the clinic. Of these, 74.9 per cent were blind within three years of the onset of symptoms, and all were blind after five years.

The second group received routine antisyphilitic therapy. Of these, 23.8 per cent were blind within three years, and all were blind eight years after the onset of symptoms. The third group received a special form of treatment, such as induced fever or subdural therapy. Of this group, 28 per cent were blind in less than three years and all were blind at the end of eight years.

<sup>3</sup> Sobanski, J. *Klin Monatsbl f Augenh* **97**:1 (July) 1936.

<sup>4</sup> Arruga, H. *Klin Monatsbl f Augenh* **97**:308 (Sept) 1936, Treatment of Atrophy of the Optic Nerve abstracted, *Arch Ophth* **18**:168 (July) 1937.

<sup>5</sup> Moore, J. E., and Woods, A. C. *Am J Ophth* **23**:145 (Feb) 1940.

<sup>6</sup> Moore, J. E., Hahn, R. D., Woods, A. C. and Sloan, L. *Am J Ophth* **25**:777 (July) 1942.

<sup>7</sup> Lehrfeld, L., and Gross, E. *Am J Ophth* **21**:435 (April) 1938.

Lehrfeld and Gross expressed the belief that ophthalmologists must look in other directions for newer methods of treatment

Bruetsch,<sup>8</sup> who examined the visual pathways of 70 patients with various types of syphilis of the central nervous system, concluded that the lesions in the optic nerve were due to an inflammatory process and that malarial therapy was the most efficacious type

However, it seems to me that the almost complete absence of foci of spirochetes in the optic nerves in the cases reported by him and by others is indirect proof that the condition is not primarily inflammatory

Biffis<sup>9</sup> reported on the autopsy observations in a case of dementia paralytica in which the optic nerves were involved. He stated the belief that the degeneration in the optic nerves was due to sclerosis of the capillaries supplying the septums of the nerve. The condition of the arterioles was not mentioned

The most recent article on the treatment of this condition is that by Knight and Schachat<sup>10</sup>. They reported 19 cases of syphilitic optic nerve atrophy in which, in addition to adequate antisyphilitic chemotherapy, treatment in the Kettering hypertherm was given. In 2 of the cases "typhoid drip" therapy was also employed. In 4 of the cases some improvement occurred, as follows

CASE 1<sup>1</sup> Vision improved from 20/20 to 20/15 in each eye, and there was an increase in the size of the peripheral fields

CASE 6 Vision improved in one eye from perception of hand movements to 4/200

CASE 8 Vision improved from perception of light to 3/200 in each eye

CASE 17 Vision was unchanged, but an increase occurred in the extent of the peripheral fields

In 7 cases there was an arrest of the clinical progression of the disease, and in 6 cases there was no arrest or the onset of symptoms actually seemed to have occurred during therapy. The duration of improvement was not stated for any of these cases

Briefly, in 21 per cent of their cases there was slight improvement in visual acuity or in the fields, and in 37 per cent, arrest of symptoms

*Vascular Basis of Syphilitic Optic Nerve Atrophy*—Because most of the treatments in vogue for syphilitic optic nerve atrophy consist in major unphysiologic insults to the body, because therapy directed against the spirochetes is inefficient and is sometimes followed by rapid loss of vision and because most of the newer types of therapy involve expensive hospitalization and loss of time for the patient and are not without danger it would seem that a revised therapeutic approach, based on the work of Abadie and others, is indicated

<sup>8</sup> Bruetsch, W. L. Malaria Therapy in Syphilitic Primary Optic Atrophy, JAMA 130 14 (Jan 5) 1945

<sup>9</sup> Biffis, A. Ann di ottal e clin ocul 65 1 (Jan) 105 (Feb) 1937

<sup>10</sup> Knight H. C., and Schachat, W. S. Arch Ophth 35 271 (March) 1946

The words of Foster Kennedy are especially significant In 1938, he stated<sup>11</sup>

It is common knowledge that vascular accidents occur in the brain in the course of untreated luetic infections The very fact that many of these episodes are rapid to occur and clear up without treatment is evidence in favor of the possibility of angiospasm being the causative mechanism Surely, luetic invasion of cerebral blood vessels must at times be an irritation adequate to set up local reflex angiospasm in these vessels

This is probably true not only of the brain but also of the eye and its adnexa Several years ago I<sup>12</sup> carried out treatment in 3 cases of paralysis of various ocular muscles and 2 cases of acute iritis in which the Wassermann reaction was 4 plus In all 5 cases intensive vasodilator

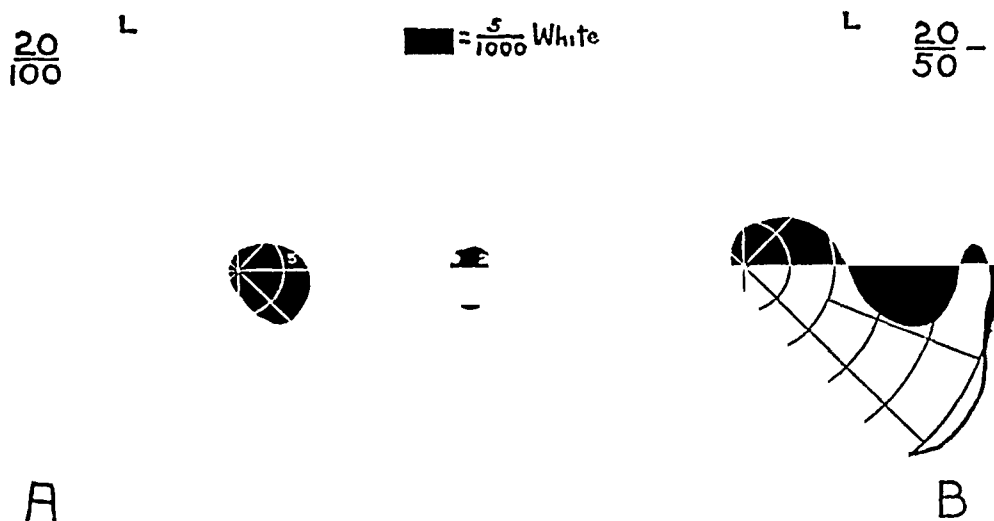


Fig 1 (case 1) —(A) Field of left eye on June 5, 1935, prior to onset of treatment with vasodilator drugs The right eye was blind (B) Field of left eye on Aug 2, 1935, after treatment The functioning field was definitely enlarged Vision was improved

In this figure, and in the accompanying figures, illumination was 10 foot candles

therapy without the use of (specific) antisymphilitic therapy effected a rapid cure of the ocular lesions

Mawas and Pinheiro<sup>13</sup> also reported a case of rapid loss of vision during a course of injections of tryparsamide A cure was obtained with injections of acetylcholine Dr Franklin Bracken described a similar case to me several years ago in which vision improved somewhat with intravenous injections of sodium nitrite

Finally Pickworth<sup>14</sup> quoted Hawes to the effect that “the later manifestations of neurosyphilis must be regarded as only a result of the vascular disease”

#### REPORT OF CASES

During the past ten years I have treated 5 patients with syphilitic optic nerve atrophy with vasodilator drugs only Although the results

11 Kennedy F New York State J Med 38:1441 (Nov 15) 1938

12 Duggan, W F Tr Am Ophth Soc 43:505 1945

13 Mawas, J, and Pinheiro, F Bull Soc d'opht de Paris 49:336 (April) 1936

14 Pickworth F A J Ment Sc 50:76 (Jan) 1941

are not astonishing, yet, because of the hopeless prognosis in most cases of this disease and because of the relatively few favorable results reported to date, it is believed worth while to bring these results to the attention of other ophthalmologists

CASE 1—J C, a man aged 60, was seen on Nov 6, 1934, at which time vision was 20/200 in the right eye and 20/70 + 1 in the left eye. Argyll Robertson pupils were present, there was bilateral primary atrophy of the optic nerve, the knee jerk was absent on both sides, there was a questionable Romberg sign, and the Wassermann reaction of the blood was 4 plus. He was referred elsewhere for treatment but failed to report for antisyphilitic therapy. On June 5, 1935 he returned to the clinic. At this time the right eye was totally blind. Vision in the left eye was 20/100, and the field was limited to a small area near the fixation point and a tiny area temporal to the region of the normal blindspot (fig 1 A).

Between June 6 and June 21, he received ten intravenous injections of sodium nitrite (100 mg). On August 2, vision was 20/50 —2 and the field (fig 1 B) was at least five times as large as it had been prior to treatment. The patient then disappeared from observation.

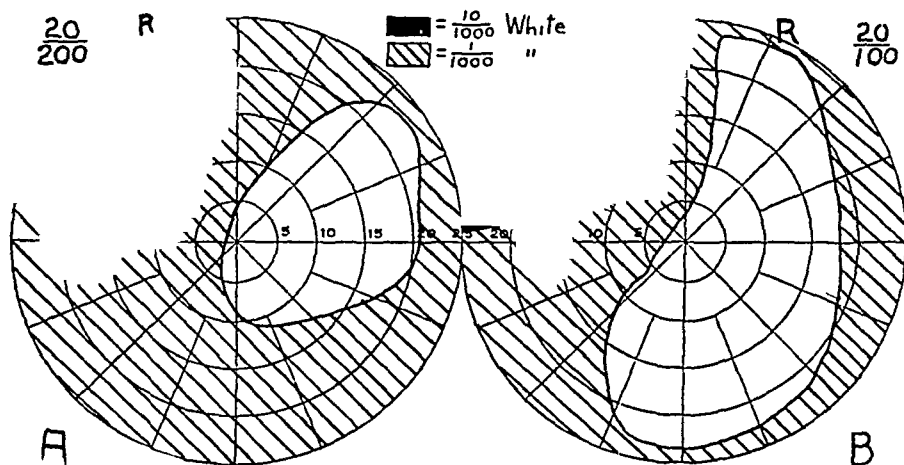


Fig 2 (case 2) —(A) Field of right eye on Aug 17, 1938, prior to treatment with vasodilator drugs. The left eye was practically blind. (B) Field of right eye on April 3, 1939, following vasodilator treatment. There was slight improvement in vision and in the field for 1/1,000 white.

CASE 2—S C, a woman aged 31, was first seen on Feb 7, 1938, with the complaint of poor vision in the right eye for six weeks and in the left eye for several years. Vision was 20/200 in each eye. Argyll Robertson pupils were present, and there was bilateral primary atrophy of the optic nerve. The upper temporal quadrant of the right field was deficient, while in the left field only the upper nasal quadrant retained vision. The Wassermann reaction of the blood was 4 plus. A roentgenogram of the skull revealed no evidence of cerebral tumor.

The patient was referred to New York Hospital, where she received malaria therapy, intravenous injections of typhoid vaccine and, finally, treatment with a bismuth compound and the arsenicals. She returned to the clinic on Aug 17, 1938, at which time vision was 20/200 in the right eye, but only 1/200 in the left eye. The right visual field (fig 2 A) was essentially the same as it had been on February 7. The field of the left eye was almost completely obliterated.

Between Aug 23, 1938 and March 27, 1939 the patient received thirty-three intravenous injections of sodium nitrite (100 mg) in series of from three to ten daily injections each. Vision in the right eye had improved to 20/100 by September 16 (after the first twelve injections) and was maintained until April 3, 1939, after which the patient failed to return for follow-up observation. The field (fig 2 *B*) showed slight, but definite, improvement in the isopter for a 1 mm white test object at 1,000 mm.

CASE 3—E H, a woman aged 58, was seen at the clinic on Oct 10, 1938, with the complaint that her lateral vision had been poor for two years. The onset occurred while she was receiving injections of trypanamide at another hospital for syphilis of

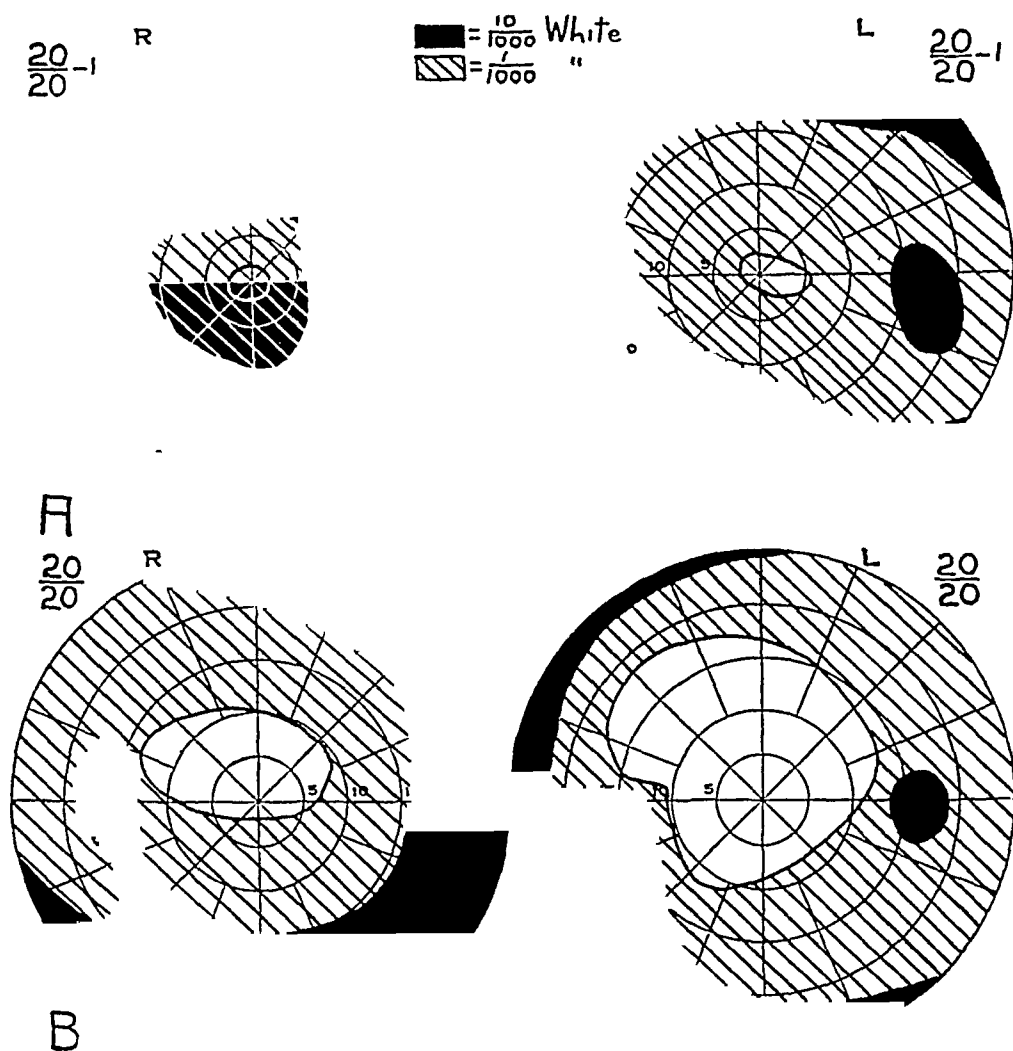


Fig 3 (case 3) —(A) Fields of right and left eyes on Oct 10, 1938, showing marked contraction of all isopters for white. Loss of visual fields occurred while the patient was receiving trypanamide in 1936. (B) Fields of right and left eyes on Jan 13, 1939, after vasodilator therapy. There was definite improvement in the visual fields.

the central nervous system. Vision was 20/20 —1 in each eye. Bilateral primary optic nerve atrophy was present. The retinal blood vessels were normal.

The fields (fig 3 *A*) were greatly contracted for 10/1,000 white, while the field for 1/1,000 white was reduced to a tiny area around the fixation point.

Between October 11 and November 23, the patient received twenty-one intravenous injections of sodium nitrite (100 mg) in three series of seven daily injections each. Fields taken at regular intervals showed steady and definite improvement. On Jan 13



1939, vision was 20/20 in each eye, and the fields (fig 3 *B*) showed a notable enlargement of the isopters for 10 and 1 mm white test objects at 1,000 mm. At this time the defect in the left field showed definite arcuate features.

In this case the loss of peripheral vision was attributed to trypanamide.

CASE 4—A B, a woman aged 55, was seen on Jan 16, 1939, with the complaint of poor vision in both eyes for ten years. She stated that vision had failed rapidly while she was being treated at another hospital for syphilis. Vision was 3/200 in each eye. Argyll Robertson pupils were present, and there was bilateral atrophy of the optic

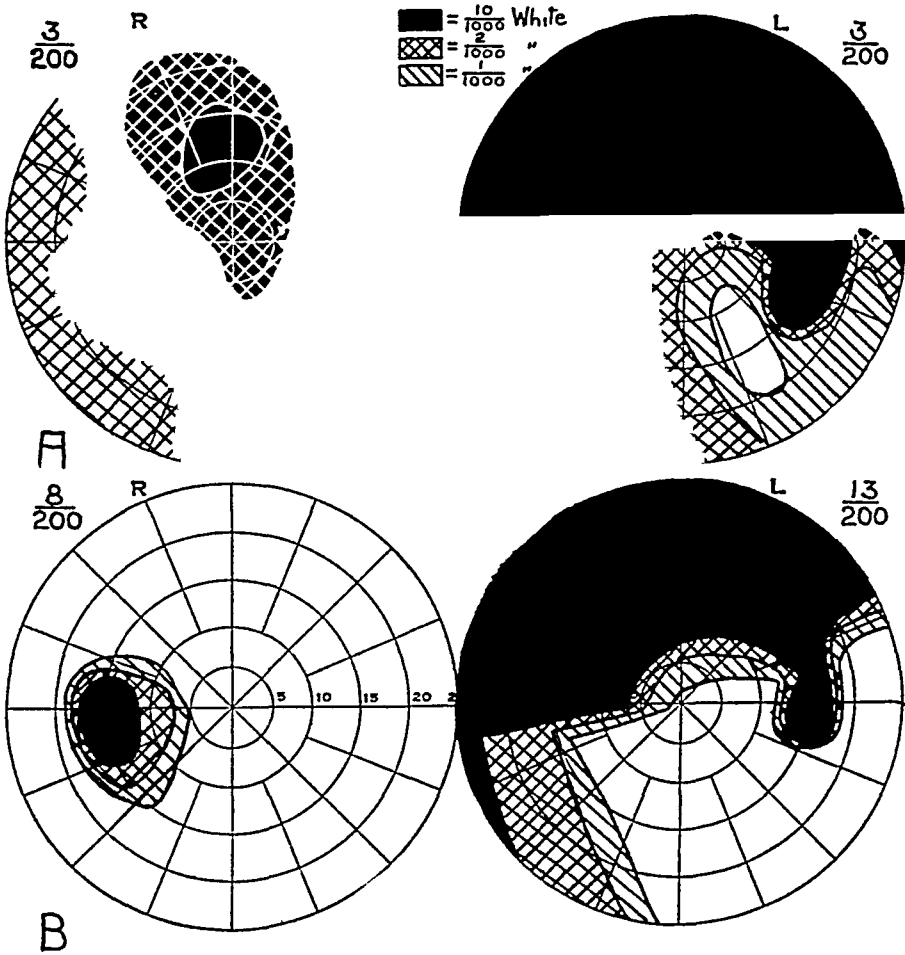


Fig 4 (case 4) —(A) Fields of both eyes on Jan 18, 1939. Vision had been poor for ten years. Visual failure occurred while the patient was undergoing antisyphilitic therapy. (B) Fields of both eyes on May 12, 1939, after therapy. Visions and fields showed definite improvement which was maintained until Sept 20, 1939.

nerve. The retinal arteries were narrowed. Tangent screen fields (fig 4 *A*) taken on January 18 showed a marked defect for 10/1,000 white. Small paracentral fields were present for 2/1,000 white in the right eye and for 1/1,000 white in the left eye. The Wassermann reaction of the blood was negative. Because of her impaired vision, the patient could not travel alone to the clinic.

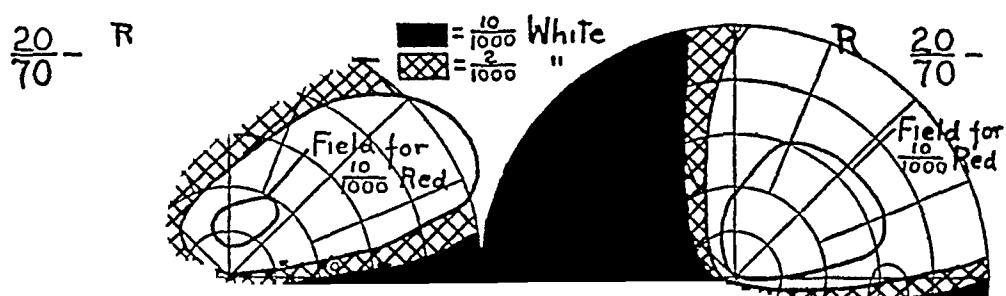
The patient received twenty intravenous injections of sodium nitrite (100 mg) between January 19 and February 9. On February 10 vision was 6/200 in the right eye and 5/200 in the left eye, the fields showed a little improvement. She was told to take  $\frac{1}{4}$  grain (0.016 Gm) of erythritol tetranitrate U.S.P. twice daily and was given eleven

more injections of sodium nitrite between February 14 and February 24. She continued the use of erythryl tetranitrate until May 12, at which time vision was 8/200 in the right eye and 13/200 in the left eye. A field taken on this date (fig 4 B) showed considerable improvement over fields taken on her admission to the clinic, prior to the onset of treatment for the optic nerve atrophy.

The patient was seen last on Sept 20, 1939, at which time her vision and fields had maintained the improvement manifested on May 12. At this time she was able to travel alone to the clinic.<sup>15</sup>

CASE 5—G M, an Italian aged 49, was seen on Nov 6, 1943. He stated that in March 1942, two weeks after a lower tooth was extracted, vision had failed in both eyes. The left eye became entirely blind in three months.

The diagnosis of syphilis was made in May 1942, and he had received several courses of antisyphilitic chemotherapy.



A

B

Fig 5 (case 5) —(A) Field of right eye on Nov 6, 1943, prior to the onset of therapy. The left eye was totally blind. (B) Field of right eye on Dec 9, 1944, after vasodilator therapy. There was definite improvement in isopters for 10/1,000 and 2/1,000 white and for 10/1,000 red. Improvement was still present on Jan 5, 1947.

Corrected vision in the right eye was 20/70 —1. The pupil was in miosis and did not react to light. The media were clear, and primary optic nerve atrophy was present. The retinal arteries were of normal caliber. A small field (fig 5 A) was present in the upper nasal quadrant. The fact that a tiny field was present for 10/1,000 red was considered to be of favorable prognostic significance.

The left eye was totally blind. Primary optic nerve atrophy was present. The Wassermann reaction of the blood was negative.

As therapy, the patient received from 100 to 150 mg of nicotinic acid, three times a day after meals, and ¼ grain of erythryl tetranitrate at bedtime.

On Feb 5, 1944 there was definite enlargement in his functioning field for 10/1,000 and 2/1,000 white. The field for 10/1,000 red improved more slowly and attained its maximum on Dec 9, 1944 (fig 5 B). Vision remained at 20/70 —1. On Jan 5, 1947 the improvement was still maintained.

<sup>15</sup> Patients 1, 2, 3 and 4 were seen and treated at the Herman Knapp Memorial Eye Hospital.

The patient discontinued the use of vasodilators in January 1946. There was apparently no further loss of vision. He was in the habit of overindulging in whisky and volunteered the information that his vision seemed to improve temporarily after a drinking bout.

#### COMMENT

While only 5 cases of syphilitic optic nerve atrophy have been described, it is of interest that all 5 patients showed improvement with intensive vasodilator therapy. None became worse. Inasmuch as the time of follow-up observation varied from two months (case 1) to three years (case 5), a statistical analysis of the results would be futile.

However, it is my opinion that the improvement manifested in these cases corroborates Kennedy's<sup>11</sup> hypothesis that in syphilis angiospasm occurs in the arterioles of the central nervous system (including the visuosensory system). Since spirochetes are rarely observed in the optic nerves and treatment of the causative factor, syphilis, does not favorably influence the progressive loss of vision, a new approach to the problem of the treatment of syphilitic optic nerve atrophy is indicated. It is not beyond the bounds of reason to hint that syphilitic optic nerve atrophy may be a manifestation of chronic allergy or a problem in morbid vascular physiology.

It can be assumed, however, that syphilitic optic nerve atrophy is not identical with the atrophy occurring in the course of tobacco amblyopia or following acute retrobulbar neuritis, in which a complete return of vision to normal is possible after a relatively prolonged period of impaired vision. In cases of syphilitic atrophy of the optic nerve, the field defects are varied and sometimes bizarre. Moreover, even a slight improvement in the visual acuity or in the size of the functioning field is regarded as a favorable result. Since total blindness is a common occurrence in cases of syphilitic optic atrophy, any type of therapy which assists in maintaining the patient's vision is of definite value.

I believe that vasodilator therapy should be used with a large series of patients, preferably in one of the state hospitals, where a greater number of such patients should be available. Only after many of these patients have been treated and followed for an adequate time will it be possible to decide whether intensive vasodilator therapy compares favorably with the various therapeutic modalities at present in vogue.

Finally, if this type of therapy is shown to be of value in improving the function of the visuosensory system, it is not unreasonable to assume that similar therapy should be of value in treating other manifestations of syphilis of the central nervous system.

## CONCLUSIONS

The results of vasodilator therapy in 5 patients with syphilitic atrophy of the optic nerve are described. No patient became worse during treatment.

All 5 patients showed improvement in the size of the functioning fields.

Three patients showed definite improvement in their visual acuity.

Similar therapy in a larger series of patients, with adequate follow-up observation, is indicated.

The ampules of sodium nitrite used in cases 1, 2, 3 and 4 were manufactured by E. Tosse & Co., a subsidiary of the Amfre Drug Company.

## DISCUSSION

DR. IVAN J. KOENIG, Buffalo, New York: The treatment of syphilitic optic nerve atrophy with vasodilators has presented not only a new therapy, but possibly further knowledge of the pathologic nature of this condition. Dr. Duggan's patients have all shown some improvement in visual acuity, which one must acknowledge, even though only 5 cases were presented.

In discussing syphilitic atrophy of the optic nerve and in evaluating its treatment, one must consider the causation and the pathologic condition. Igersheimer showed that the atrophy was accompanied with a slight perivascular round cell infiltration in the meninges of the optic nerve. Spirochetes were seen in these infiltrates, but rarely in the optic nerve, where focal lesions of degeneration were present.

The exact nature of the pathologic process is still in dispute. It is assumed that the optic nerve sheaths present an inflammatory infiltrate, which is followed by secondary degeneration of the optic nerve fibers and their ganglion cells. Foster Kennedy assumed that some vasoconstriction of the arterioles is present. This seems to be a logical conclusion, as such a constriction could be produced by the inflammatory reaction. If this theory is true, the value of vasodilator therapy would be proved, and its use may account for the improvement in the color of supposedly atrophic disks.

Ophthalmoscopically, there are times when it is difficult to determine the amount of atrophy of the nerve, and when the question arises: Is this atrophy or pallor? Sloan and Woods reported certain field defects typical of tabetic atrophy with normal-appearing disks, which remained so for five years after changes in the fields had begun. Many clinicians and pathologists agree with Duke-Elder that "when actual optic atrophy has occurred, it is permanent." This statement of Duke-Elder's raises the question: How often can atrophy be recognized in sections of the optic nerve which shows pathologic pallor with the ophthalmoscope? Relief of the vasoconstriction may be the real answer to improvement in color, vision and field defects, but is it effective with true atrophy?

Many therapeutic measures may be used to produce vasodilation, among which are fever therapy (after its initial vasoconstriction), dia-

thermy, and administration of vitamin B complex, amyl nitrite, glyceryl trinitrate and acetylcholine in addition to the drugs which Dr Duggan has mentioned

I have used sodium nitrite considerably in cases of disease of the optic nerve with pallor from some cause other than syphilis, with good results I have not treated atrophy caused by syphilis with the drugs Dr Duggan mentioned

When asked to discuss this paper, I went over my records in search of cases of tabetic atrophy I was surprised to find so few I found 2 cases in which malarial treatment was given, with improvement in the field defects after treatment In 1 case the visual improvement was maintained for six years, and in the other, for five years This brings to mind a report of Woods and Moore, who claimed that 85 per cent of patients with one good eye (20/40) and a good visual field will show improvement in vision if given adequate malarial treatment The remaining 15 per cent of patients will go blind in three years Since malarial therapy is the accepted treatment of syphilologists, it might be wise to add vasodilators to their therapeutic armamentarium

It is my feeling that syphilitic optic nerve atrophy will become a rare disease, for the treatment of early syphilis is being carried on more efficiently than ever before and this early treatment is the best way to avert the complication of optic nerve atrophy

Before closing, I feel that some contraindications to sodium nitrite and erythrityl tetranitrate should be mentioned I have used both these drugs, with therapeutic benefit, in other types of cases Sodium nitrite does increase the intraocular tension in some cases of glaucoma and pre-glaucoma and should be used with discretion in such cases Erythrityl tetranitrate, when used, frequently causes severe headaches, and the dose must be varied in some cases A tolerance to vasodilators often becomes evident after two or three weeks' use, and a regimen of periods of rest with intermittent treatment is more advantageous than continued treatment with these drugs

When using acetylcholine as a vasodilator, I have observed that the bromide salt gives a less severe general reaction than the chloride salt In order to complicate a situation for more discussion, I should like to quote Best and Taylor, who, in 1945, stated that sodium nitrite causes vasoconstriction of the arterioles and that the fall in blood pressure is due to venous dilatation

# IMPLANT OF "VITALLIUM" TUBE IN TREATMENT OF STENOSIS OF THE LACRIMAL DUCT

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In the last two decades, the operation of choice in treatment of stenosis of the lacrimal duct has been dacryocystorhinostomy, with the more or less modified technics of Toti and Dupuy-Dutemps. Though the results of these operations have been encouraging, there is still a high percentage of failures, due mostly to alteration of the nasal mucosa in atrophic rhinitis and ethmoiditis and to technical difficulties in the operation. A much simpler procedure is the insertion of a "vitallium" tube into the bony lacrimal duct through the lower part of the sac, as advocated by Muldoon<sup>1</sup>

"Vitallium" is an alloy composed of cobalt, 65 per cent, chromium, 30 per cent, and molybdenum, 5 per cent. It is free from chemical and electrolytic activities in human serum and when buried in human tissue does not produce any of the inflammatory reactions of other metallic foreign bodies<sup>2</sup>. It is used chiefly in bone surgery but is employed as in other surgical fields. The tube devised by Muldoon is 3 mm in diameter and 18 mm in length, with the lower end slightly tapered. I have used this model successfully in several cases of stenosis, but its failure in a case in which the tube, though properly placed, slipped into the bony lacrimal duct convinced me of the necessity of certain modifications.

In order that the implant may be held in its proper position, the new tube<sup>3</sup> is made with a holding loop 4 mm from the opening of the tube into the lacrimal sac (fig 1) and a small ring at the upper end. The loop serves a twofold purpose, first in permitting a surgical gut suture to be passed through the hole to be attached to the periosteum of the nasal bone, and, second, in widening the upper part of the tube to 5 mm, thus preventing its slipping down into the bony canal. Moreover, the tube is 24 mm long, and about 4 mm of its upper end is inserted into the lower part of the lacrimal sac.

The operation is usually performed with the use of local anesthesia, obtained by infiltration of the area of the lower part of the lacrimal sac with "solution of procaine hydrochloride 2 per cent with epinephrine" and injection of a few drops of cocaine,

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1 Muldoon, W E. Restoration of Patency of the Nasolacrimal Duct by Means of a Vitallium Tube, *Am J Ophth* **28** 1340, 1945

2 Venable, C S, and Stuck, W G. Electrolysis Controlling Factor in the Use of Metals in Treating Fractures, *J A M A* **111**:1349 (Oct 8) 1938. A General Consideration of Metals for Buried Appliances in Surgery, *Surg, Gynec & Obst* **76**:297, 1943

3 This tube is manufactured by Austenal Laboratories Inc. 224 East Thirty-Ninth Street New York

4 per cent, into the sac. The sac is washed with saline solution, and a Bowman probe is passed until it reaches the stricture in the duct. The purpose of this probe is to serve as a guide in the dissection and exploration of the duct. An incision, 1.5 cm long, is made in the skin, starting at the lower part of the inner canthal ligament, which is left intact. The incision is carried down through the fibers of the orbicularis muscle and the deep fascia to reach the lower part of the sac, with the probe as a guide. A small incision is made in the sac and the bony canal is curetted, after which the "vitallium" tube is inserted and pushed down, leaving about 4 mm of it, which is inserted into the lower end of the lacrimal sac.

The probe, which was partially withdrawn during the insertion of the "vitallium" tube, is now pushed down through the tube into the nasal cavity. A 000 surgical gut suture is passed through the holding loop and secured to the periosteum. Another small suture closes the sac over the tube, while the cutaneous wound is closed with silk. The probe is removed, and the lacrimal passages are irrigated with saline solution to ascertain their patency. A light compression bandage is applied, and the patient is discharged in twenty-four hours.

This procedure was used in 3 cases in which there were mucopurulent discharges from the puncta on compression of the sac.

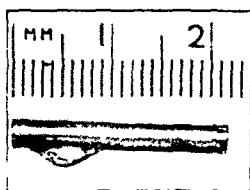


Fig 1—Vitallium tube, La Rocca type

#### REPORT OF TWO CASES

**CASE 1**—A D F, a woman aged 54, complained of stenosis and purulent chronic dacryocystitis of the left eye of seven years' duration. The sac had been probed at several clinics and by private physicians. The patient was first seen in my office on Feb 3, 1946, at which time there was a mucopurulent discharge on pressure on the region of the lacrimal sac, both canaliculi were present. Probing was unsuccessful and very painful because of an obstruction at the upper end of the bony lacrimal duct.

The patient was admitted on Feb 15, 1946 to the New York Eye and Ear Infirmary, where a "vitallium" tube, of the Muldoon type, was inserted. Irrigation soon after the closure of the wound showed patency of the lacrimal passage. At the first dressing, a few days later, some discharge was still found in the sac, and irrigation showed that an obstruction had already formed. Probing through the tube was not attempted until about a week later. When it was found impossible to pass a probe through, a roentgenogram was taken (fig 2), which showed displacement of the tube. The patient was readmitted on July 10. All attempts to raise the tube failing, a dacryocystectomy was performed, leaving the tube buried in the bony canal. Recovery was uneventful, epiphora persisted.

**CASE 2**—R V, a woman aged 62, had had epiphora and discharge from the sac of the right eye for the past two years. Only a few probings were attempted because of excessive sensibility. An occlusion was found at the beginning of the bony lacrimal duct. After several unsuccessful probings, the patient was admitted on July 2, 1946 to the



Fig 2 (case 1) —Bowman's probe stops about 3 mm from the upper opening of the tube



Fig 3 (case 2) —Probe passes through the sac and tube into the nasal cavity



Columbus Hospital, where a "vitallium" tube, La Rocca type, was implanted, according to the technic previously described. She was discharged within twenty-four hours. At the first dressing, three days later, there was no discharge, and irrigation demonstrated the patency of the passages. A roentgenogram showing the tube in place with a Bowman probe passing through is shown in figure 3.

#### COMMENT

The implant of the La Rocca "vitallium" tube of the type described offers the following advantages:

- 1 The tube cannot slip into the nasal cavity because the upper end has a larger diameter than that of the bony canal.

- 2 It can be performed in any case of stenosis of the lacrimal duct with or without dacryocystitis, for, the patency being once established, the drainage takes care of the infection of the sac.

- 3 The operation is much simpler than the dacryocystorhinostomy.

- 4 Intranasal infections and atrophy of the nasal mucosa are not obstacles to implantation of the "vitallium" tube.

- 5 The operation can be easily performed with local anesthesia.

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# INTRAOCULAR PRESSURE IN CASES OF HEMORRHAGE OF THE RETINA

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My interest in the relation of intraocular pressure to hemorrhages of the retina was awakened by an article by Igersheimer,<sup>1</sup> and I began a systematic study of the tonometric readings of the eye in all patients sent to me for ophthalmologic examination with diseases in which complications involving the retina are frequent, the most important of these being retinal hemorrhage.

Igersheimer, after a brief discussion of the physiology of the eye, maintained that pressure outside the vascular walls, represented in the eyeball by the intraocular tension, may have an appreciable influence on the passage of fluid through the walls of the vessels. Only in certain conditions can this pressure be increased without the use of artificial methods. These conditions are fulfilled in the case of closed cavities, such as the eye or the cranium. I shall not discuss the observations and clinical details on which he founded his hypothesis, since the present paper does not purport to be more than a statistical contribution to strengthen or to correct his assertion.

I shall present the results obtained in a series of 215 patients, of whom 51 had hypertension but no retinal signs of vascular sclerosis, 129 had hypertension with retinal signs of vascular sclerosis and 33 had hypertension with definite renal involvement. One had arteriosclerosis but no hypertension, and another had retinal phlebitis with hemorrhage of tuberculous origin.

In a previous paper I showed the results obtained on 99 patients with diabetes. Thus, I have a total of 314 patients with or without retinal hemorrhage whose intraocular pressures have been systematically determined in order that the tonometric measurements may be correlated with the presence or absence of retinal hemorrhages.

Though the number of observations is small, it is large enough to give an idea of the relation of these two factors, and I can confirm to a great extent the opinion expressed by Igersheimer.

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<sup>1</sup> Igersheimer, J. Intraocular Pressure and Its Relation to Retinal Extravasation, *Arch Ophth* 32:50 (July) 1944.

In my investigations, I followed the directions given by Vidal and Damel<sup>2</sup> I consider that the tonometric readings obtained with the Schiotz apparatus indicate that 19 mm represents normal tension, from 15 to 18 mm physiologic hypotension and from 20 to 25 mm physiologic hypertension Values below 15 mm indicate pathologic hypotension, and values above 25 mm, pathologic hypertension

The tensions were determined at 9 to 11 a m Tetracaine hydrochloride, 0.5 per cent, was used as an anesthetic, and the measurement was made quickly and neatly once, with the Schiotz tonometer in order that the threshold of elimination should not be increased by the weight of the tonometer The emotional state of the patient was taken into consideration

In this series of 215 patients, 148 had no retinal hemorrhages (295 eyes were examined, as 1 patient had had an eye removed) The tonometric figures obtained for these patients are shown in table 1

TABLE 1—*Tonometric Readings on Eyes with No Retinal Hemorrhages*

Intraocular Tension, Mm	No of Eyes	Percentage of Total Series
0-14	8	2.7
15-18	57	19.3
19	94	31.7
20-25	125	42.3
25	11	3.7

TABLE 2—*Tonometric Readings on 134 Eyes With Retinal Hemorrhage*

Intraocular Tension, Mm	No of Eyes	Percentage of Eyes (134)
0-14	5	3.7
15-18	49	36.5
19	37	27.6
20-25	42	31.3
25	1	0.7

Of these 215 patients, 67 showed retinal hemorrhages (134 eyes examined) The tonometric readings are shown in table 2

Examination of tables 1 and 2 reveals the suggestive fact that the frequency of low readings is remarkably higher in eyes with retinal hemorrhages (40.2 per cent) than in eyes without such hemorrhages (22 per cent) It seems, therefore, that ocular hypotension (either physiologic or pathologic) predisposes the eye to hemorrhages of the retina

In a series of 99 patients with diabetes on whom a similar study was carried out, 51 had no retinal hemorrhages (102 eyes examined), the tonometric readings being shown in table 3

Of these 99 diabetic patients, 48 showed retinal hemorrhages (96 eyes) The tonometric readings are shown in table 4

2 Vidal, F, and Damel, C S Sistema neuro-vegetativo ocular Tension ocular normal, Arch de oftal de Buenos Aires 19 212 (April-May) 1944

Examination of these tables confirms the salient observation on the first group, namely, that low tonometric readings (either physiologic or pathologic) are more frequent in eyes with retinal hemorrhage (38 per cent) than in eyes in which hemorrhage has not occurred (22.5 per cent)

When all the cases in which retinal hemorrhages were not present (cases of diabetes, hypertension and arteriosclerosis) are tabulated with all cases in which they occurred, the low tonometric readings show a similar greater frequency in the latter (table 5)

TABLE 3—*Tonometric Readings on Eyes of Diabetic Patients With No Retinal Hemorrhage*

Intraocular Tension, Mm	No of Eyes	Percentage of Eyes (102)
0-14	4	3.9
15-18	19	18.6
19	21	20.5
20-25	54	52.8
25	4	3.9

TABLE 4—*Tonometric Readings on Eyes of Diabetic Patients with Retinal Hemorrhage*

Intraocular Tension, Mm	No of Eyes	Percentage of Eyes (96)
0-14	10	10.4
15-18	27	28.1
19	23	23.9
20-25	29	30.2
25	7	7.2

TABLE 5—*Tonometric Readings on Eyes of All Patients*

Intraocular Tension, Mm	No of Eyes	Percentage of Eyes
	Patients With Hemorrhages (397 Eyes)	
0-14	12	3.02
15-18	76	19.14
19	115	28.96
20-25	179	45.08
25	15	3.77
	Patients Without Retinal Hemorrhage (230 Eyes)	
0-14	15	6.52
15-18	76	33.04
19	60	26.08
20-25	71	30.86
25	8	3.47

The results of this investigation of 314 patients with diseases in which hemorrhage of the retina is a frequent symptom (627 eyes examined, as 1 patient had had one eye removed) may be summarized as follows. The intraocular tension (both physiologic and pathologic) is lower in patients with retinal hemorrhages (39.5 per cent) than in patients without such hemorrhages (22.1 per cent). From this, it may be concluded that a low intraocular pressure may predispose to the production of hemorrhage, for which reason a tonometric reading on patients with diseases in which retinal hemorrhages is a frequent complication is of definite value in the prognosis.

Although I do not wish to claim an absolute value for this conclusion, which may be invalidated by the relatively small number of cases

observed, it is evident that there is a certain relation between the intraocular tension and the appearance of retinal hemorrhage

Since arteriolosclerosis tends to lower the intraocular tension<sup>3</sup> and phlebosclerosis to raise it, it is important in making a prognosis to know which of the two conditions is predominant in the case, as well as to determine the intraocular tension itself. With arteriosclerosis, the tension is lowered as the inflow of blood is decreased, owing to the diminished caliber of the arterioles, the decreased circulation, in turn, influences the production of the aqueous humor (if the theory is accepted that the latter is the result of dialysis). With phlebosclerosis, the tension is raised because of obstruction in the mechanism of elimination (venous capillaries and distributing veins).

In order to make this differentiation, the neuroarteriolar test devised by Vidal and Damel<sup>4</sup> and the neurocapillary test, proposed by Vidal and Malbran,<sup>5</sup> can be used, as well as the ophthalmologic examination.

The conclusions to be drawn from the present investigation are similar to those in my previous study.

- 1 The percentage of low ocular tonometric readings, both physiologic and pathologic, is suggestively higher in patients with hemorrhage of the retina than in patients in whom it does not exist.

- 2 Many of the cases in which retinal hemorrhages exist and the ocular tonometric readings are physiologically or pathologically high can be explained by the extent of the vascular alterations, against which the external pressure is insufficient to counterbalance or to withstand the passage of fluid.

- 3 In some cases a good vascular condition compensates for the predisposition revealed by low tonometric readings, and hemorrhage is not produced.

- 4 The prognostic value of the tonometric readings for patients whose vascular condition predisposes to retinal hemorrhage is increased if the predominant type of vascular sclerosis can be ascertained when such sclerosis exists.

- 5 Low tonometric readings can be related to predominance of arteriosclerosis and high readings to predominance of phlebosclerosis.

Hospital de Caridad

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3 Vidal, F., and Malbran, J. *Oftalmotono dinamico y arterioloesclerosis retiniana*, Arch. de oftal. de Buenos Aires **20** 240 (June) 1945.

4 Vidal, F., and Damel, C. S. *Sistema neuro-vegetativo ocular. Test neuro-arteriolar*, Arch. de oftal. de Buenos Aires **19** 297 (Aug.) 1944.

5 Vidal, F., and Malbran, J. *Sistema neuro-vegetativo ocular. Test neuro-capilar*, Arch. de oftal. de Buenos Aires **20** 408 (Oct.-Dec.) 1945.

## POSTMORTEM OCULAR PRESSURE

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The ancient Greeks, and Romans too, were well acquainted with the ocular phenomena of death. They are mentioned by Hippocrates, Galen and others. The artistic exhibition generally preceded the scientific description. One can see the postmortem immobility of the eyes in a turned-up position in the far famed picture of Guido Reni "Saint Sebastian," painted many hundreds of years before the scientific description. The first enumerations of postmortem ocular phenomena were made by Antoine Louis and, a little later, by Bichat. Most ancient investigators were interested only secondarily in scientific causes, their main motive was in agreement with the spirit of the age, to determine the real and absolutely sure sign of death. So great was the fear of cataleptic trance in those days that apprehension was not groundless. In this connection, interesting data may be found in the book of the famous Hyrtl.

Antoine Louis, in 1752, attributed an extraordinary significance to the sinking and softening of the eyeballs. According to his view, as long as the eye retains its normal firmness, the patient should not be declared dead, whatever other signs are present. The sinking and softening of the eyeballs prepare one for the subsequent putrefaction. It is natural that these statements did not stand without contradiction. Josat<sup>1</sup> (1854) emphasized that many patients survived the appearance of this phenomenon by nine days. Josat pointed out that the eyes, like other organs, attempt just before death to regain their former state, including the intraocular pressure. Ortila stated that in many cases of anaphylaxis the softened eyes became harder. In still other cases the formerly soft eyes became harder after death. The Marquis d'Ourches, in 1872, left a large sum for the discovery of a certain sign of death, and many prize essays arrived at the medical school. Devergie reported on these papers and discussed also the ocular pressure after death. He did not trust this ocular sign and noted many diseases in which a fall in ocular pressure was observable in life.

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This paper appeared first in the Hungarian literature in 1939. The author was then assistant at the University Eye Hospital, Prof. L. de Blaskovics, Director. The author is not able to give the exact data for all the literature cited, as all his notes were lost during the war.

1 Josat, A. *De la mort et de ses caracteres*, Paris, Germer-Bailliere, 1854.

Stellwag made the closest observation on postmortem changes in the eyes. He cited Coccus, who stated that if the glaucomatous eye was protected from desiccation it maintained its pressure for many days. Stellwag explained this by the rigidity of the sclera and the increased pressure in the intraocular veins. Albrand, an expert in postmortem ocular signs, stated that the ocular pressure becomes negative soon after death. He mentioned as a cause of this fall in tension the desiccation and the decrease in intraocular fluids. In ancient legal medicine, it was stated that the tension in the eyes was restored in the state of advanced putrefaction. Bouchut could not confirm this statement. Silbersteiner noted that the eye of a drowned man maintained its tension. This assertion was verified by the experiments of Baillart,<sup>2</sup> Sedan<sup>3</sup> and Diaz Dominguez,<sup>4</sup> who placed the eye in distilled water and found that the pressure returned, whereas the pressure sank in a hypertonic solution.

Most of these observations were made before the time of the tonometer. Since the testing of ocular pressure by means of palpation is open to many errors, this method is to be applied only with care. Leber, who made exact manometric measurements on animal eyes, obtained the following interesting results. On the death of the rabbit from bleeding, there was a sudden drop in ocular pressure, from 18.5 to 9 mm. of mercury. The pressure fell also at the moment of cessation of artificial respiration in curarized animals, even if it was high before, the average decrease being 8 to 12 mm. of mercury. Then followed a more gradual decrease. The cause was not the drop in blood pressure but the escape of the intraocular fluids.

Krause observed the enormous fall in tension in patients in diabetic coma and in cadavers. "It is generally thought that in moribund patients and in the cadaver a strong decrease in the tension is the rule, but this is not so. In recent years, I have measured the tension in more than two dozen moribund persons and cadavers and have never observed hypotony, such as occurs in diabetic coma." Krause's observations were made before the introduction of the tonometer.

Enucleation means the death of the eye, therefore, the measurement of tension in enucleated eyes is a suitable method by which to answer the question of ocular tension after death. Hamburger measured the tension just before and after enucleation. Of 9 nonglaucomatous eyes, 1 eye showed a decrease in pressure from the original 22 mm. of mercury to 16 mm., but the tension in the others fell to zero in nine minutes, the reverse of the condition in the 11 glaucomatous eyes, of which only 1 lost its tension entirely after enucleation, the others preserving 16 to 60

2 Baillart. Imbibition de l'oeil enuclee, *Rev. gen. d'opht.* **40** 50, 1926.

3 Sedan, J. Note sur l'imbibition d'un globe hypotone, *Rev. gen. d'opht.* **40** 89, 1926.

4 Diaz Dominguez, D. Etude sur l'imbibition de l'oeil nuclee, *Ann. d'ocul.* **163** 183, 1926.

per cent of the original pressure In 1 case, even after four hours, the pressure measured 3 mm of mercury

Smith<sup>5</sup> found that blind glaucomatous enucleated eyes not only were hard at the moment of fixation but remained so a long time, proving that the high ocular pressure is not due to the blood pressure alone Jacobson,<sup>6</sup> in 1884, stated that the glaucomatous eye retains its hardness after enucleation longer than the normal eye Elliot, in the examination of 4 glaucomatous eyes, found that when the scissors were passed straight back to the optic nerve and free bleeding took place, the tension fell to 35 mm, whereas it previously had been 55mm Smith, in his reply, mentioned a case in which the right (glaucomatous) eye twenty-four hours after death was still harder than the other eye, and after enucleation was still harder than the fellow eye Elliot observed that if a glaucomatous eye is thrown on the floor after removal it bounces

I also measured the tension of the glaucomatous eye after removal, and I agree with the statements of Coccius, Stellwag, Priestley, Smith and others There is no difference in the tension of the eye with primary glaucoma and that of the eye with secondary glaucoma This observation was also shown in the tables of Hamburger<sup>7</sup>

The measurement of tension in the enucleated eye does not meet with any obstacle More difficult is its measurements with the eye *in situ*, in the orbit In accordance with the observations in Valude's investigations and in mine,<sup>8</sup> the eyes are rolled up and fixed after death and the cornea is partly covered with the upper lid Before the onset of rigor mortis, while it is easy to open the eyelids, the tonometer cannot be correctly placed

The response of the tension in the death agony is also interesting, but its determination is not simple The head is in constant movement from the forced inspiration, and the eyes are turned upward In trying to bring the eyes down with the forceps, one produces a change in tension For unconscious patients and for those who are not able to control the voluntary movements of the eyes the Fick-Livschitz tonometer seems to me the most suitable It has a spring and can also be applied to the sclera Fernbach, at Hamburger's suggestion,<sup>9</sup> measured the tension on 4 cadavers fifteen to thirty minutes after death The tensions in the eyes measured 0, 1.5 and 2, 2 and 2.5, and 5 and 5 mm, respectively

My first case was that of a woman aged 68 with diabetes who died of myocardial degeneration Two days before death tension in the eyes measured 11 and 12 mm of mercury one minute after death it was 6 mm of mercury in each eye, five minutes after death 4.5 mm and forty minutes after death, 1.5 mm

<sup>5</sup> Smith, P. Glaucoma Problems, *Ophth Rev* **29** 289, 1910

<sup>6</sup> Jacobson J, Sr. Klinische Beiträge zur Lehre vom Glaukom, *Arch f Ophth* **30** (pt 1) 165, 1884

<sup>7</sup> Hamburger C. Grundsatzliches zur Lehre vom Glaukom, *Klin Monatsbl f Augenh* **87** 638, 1931

<sup>8</sup> Majoros J. Totenstarre der Augenmuskeln *Arch f Ophth* **134** 112, 1935



The second case was that of a woman aged 58 with diabetes, who died of cardiac weakness, without coma or acidosis. The tension two days before death was 16 mm in each eye, and two minutes after death it measured 2 and 4 mm in the respective eyes.

The third case was that of a woman aged 72 who died of pulmonary embolism. Eight days before death the tension was 20 mm in each eye, twenty minutes post mortem it was 15 and 13 mm, respectively.

In the first 2 cases I attempted, unsuccessfully, to measure the tension during the agony.

These cases confirm the observation of Leber that low ocular pressure occurs after death, not only experimentally in animals but also in man. The remaining pressure is lost over a relatively long period, there may be a difference between the tensions in the two eyes.

Preservation of the tension in the glaucomatous eye permits the important conclusion that the pressure in the glaucomatous eye is independent of the vascular pressure, i.e., the blood pressure exerts only a small, direct influence on the ocular pressure. When and why this independence begins in the glaucomatous eye is not understood. It is well known that the high ocular pressure falls with sudden weakness, showing that in some cases this independence of the ocular tension may break down abruptly.

In consideration of the factors which play a part in the postmortem fall of ocular pressure, it is logical to conclude that the primary fall is due to the loss of blood pressure. Koster showed that an increase of 0.007 in the ocular contents is followed by an increase in pressure of from 19 to 70 mm of mercury. This statement is in accordance with Racevskij's<sup>10</sup> observation that the injection of 0.02 cm of fluid raised the tension to 60 mm of mercury. There is no question that the vitreous plays an important role in the postmortem ocular pressure.

#### SUMMARY

The ocular pressure falls at the moment of death, but some pressure remains. This residual pressure then disappears slowly. There may be a difference in tension between the two eyes. This postmortem change in the ocular pressure is not a safe and sure diagnostic sign of death. In numerous ophthalmic and general diseases the pressure is sometimes as low as it is in death. After enucleation the tension generally becomes zero. The glaucomatous eye retains its pressure after death and after enucleation. The primary decrease is due to the change in the vitreous. Tension in the eye with primary and that in the eye with secondary glaucoma act in the same way.

VIII Brody Sandor-u-6

9 Hamburger, C. Tonometrische Beiträge zur Lehre vom Glaukom, *Klin Monatsbl f Augenh* 67:643, 1921.

10 Racevskij, *Zentralbl f d ges Ophth* 43:574, 1939.

# CONGENITAL HYPOPLASIA (PARTIAL APLASIA) OF THE OPTIC NERVE

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AND

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PHILADELPHIA

We are reporting 2 cases of a congenital anomaly which is rare when occurring in an otherwise normal eye Scheie and Adler<sup>1</sup> (1941) reviewed the literature on the subject, finding 5 cases of partial aplasia of the optic nerve reported up to that time, and added 1 of their own. Another paper on this subject has since been published in Brazil.<sup>2</sup>

A brief review of the embryology of the optic nerve will facilitate understanding of the possible causes of the anomaly.<sup>3</sup> The optic vesicle becomes the optic cup, beginning at the 4.5 mm stage of development. This is brought about by the invagination of the outer wall, the future retina, to approximate the inner wall, the future pigment epithelium. Coincidentally, the fetal fissure forms along the ventrolateral surface of the optic cup and stalk. Mesodermal tissue then invades the optic cup through the fetal fissure, filling the optic cup with embryonic blood vessels, the hyaloid system, and forming the primitive papilla. Fusion of the fetal fissure begins at the 10 mm stage and is soon complete. At the 17 mm stage the retinal ganglion cells appear, their axons piercing the primitive papilla and forming the neural elements of the optic nerve. The primitive papilla is thus enlarged by the cross sectional area of the nerve fibers to the size of the fully developed papilla. The axons of the retinal ganglion cells reach the optic chiasm at the 18 mm stage. Here, there is a partial decussation of the fibers, and at the 25 mm stage they have reached the lateral geniculate body through the optic tracts. There are two possible explanations for the failure of normal development of the optic nerve, other ocular structures being normal.

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From the Department of Ophthalmology, Hospital of the University of Pennsylvania

1 Scheie, H G, and Adler, F H. Aplasia of the Optic Nerve, *Arch Ophth* 26:61 (July) 1941

2 Rocha, H. Hipoplasia do nervo optico, *Arq brasil de oftal* 8:1 (Feb) 1945

3 Mann, I C. The Development of the Human Eye, London, Cambridge University Press, 1928

1 If for some reason the growth of mesoderm into the fetal fissure is delayed, the latter may fuse completely, thereby preventing any hyaloid, or later retinal, blood vessels from entering the eye. Complete aplasia of the optic nerve, with no papilla, retinal vessels or retinal ganglion cell layer, results.

2 If, for any reason other than defective blood supply, the retinal ganglion cells fail to develop, an abnormally small disk with normal retinal vessels may result, i e., hypoplasia of the optic nerve. The visual field defects reported in some of the cases in the literature would presumably correspond to failure of development of the retinal ganglion cells, and the size of the papilla would depend roughly on the percentage of the axons of the ganglion cells present.

In the authentic cases reviewed and reported by Scheie and Adler<sup>1</sup> in which this anomaly of the optic nerve was present in otherwise normal eyes, clinical evidence supporting this theory of the mechanism of development of hypoplasia of the optic nerve is given. This anomaly may be unilateral or bilateral. These authors also reviewed a case reported by Krause (1920) which was apparently one of complete aplasia, without papilla or retinal vessel funnel, but the eye had 14 D of myopia due to ectasia in the region where the optic nerve should have been. This observation suggests that complete aplasia of the optic nerve is not compatible with an otherwise normal eye. Scheie and Adler reported a total of 6 cases of hypoplasia—5 from the literature and 1 of their own.

#### REPORT OF CASES

CASE 1—D. C., a Negro aged 24, a cow herder, was referred from the neurologic clinic on Dec. 11, 1946, because of nystagmus and poor vision. Treatment for epilepsy of four years' duration, with both petit and grand mal attacks, was being given, with recent notable reduction in the frequency of the attacks. The patient had been blind in his right eye since birth.

He stated that his birth had been normal and spontaneous. His only disease in childhood had been uncomplicated measles. The family history did not include cases of epilepsy, ocular disease or any condition pertinent to his present ailments. All 10 siblings were living and well.

Objective examination—physical, mental and neurologic—revealed no significant abnormality except for his eyes. The Kolmer and Kline tests of the blood for syphilis gave negative reactions. Electroencephalographic studies showed a general level of cerebral activity within normal limits.

Ocular examination revealed light perception only in the right eye, with visual acuity of 6/15, correctible to 6/15 + 3 with a -1.75 cyl axis 35 in the left eye. Ocular rotations were full and the eyes straight. A transient, coarse ocular nystagmus of the type frequently seen with defective vision was present, and it increased in intensity during examination of the eyes. Both pupils reacted slowly to light and normally in accommodation.

On ophthalmoscopic examination the media appeared clear. The disks were nearly round, each being about two-thirds normal size. They appeared to be dead white ex-

cept on the nasal sides. The nasal side of the right disk was greenish white. The disk was obliquely placed and inclined steeply to the temporal side. The nasal side of the left disk was pale gray and similar in conformation to its fellow. A cilioretinal vessel emerged from its edge. Both disks had a heavy temporal pigment conus. After leaving the nasal side of the disk, the vessels destined for the temporal portion of the retina arched nasalward in wide sweeps before bending temporally. The vessels were of almost normal caliber but gave off few small branches. No abnormalities of the macular area or of the rest of the retina were noted in either eye.

The only field obtainable in the right eye was with a bright light, and this was smaller than normal in all meridians. Light projection was good in all meridians. The peripheral field of the left eye showed conspicuous contraction in the superior temporal sector to 1 and 10 mm white test objects at 330 mm. The findings in the central field in this eye were consistent with the changes in the peripheral field, 2 mm white and 20 mm red test objects at 1,000 mm being used. It seems reasonable to attribute these field defects to the deficiency in the formation of the neural elements evolving from the primitive ganglion cell layer, referred to in the introduction to this paper.

CASE 2—W D, a 6 month old white infant, was brought to us by his parents, who stated that he did not notice or follow objects and was apparently blind. Birth was at full term, and delivery was normal. Three other children of the same parents were all said to have normal vision.

General physical examination by members of the pediatric department of the hospital revealed no significant abnormalities. A roentgenogram of the skull was reported to be normal. External examination of the eyes and adnexa revealed nothing abnormal. Ocular rotations were full. The eyes were straight, and there were no nystagmoid movements. The pupils were round, equal and of moderate size. There were prompt direct and consensual light reflexes in each eye and good dilation with homatropine. Ophthalmoscopic examination revealed no appreciable refractive error and the media were normal. The optic disks were small, being about one-third normal size, round and cupped, with a gray pigment crescent nasally. The retinal vessels were present and normal in the number of branches, the caliber of both arteries and veins being somewhat smaller than normal. No lesion was seen in the fundus of either eye, and no definite macular abnormalities were visible with an ophthalmoscope.

In summary, there was no ocular abnormality except bilateral hypoplasia of the optic nerves.

#### COMMENT

These cases represent bilateral hypoplasia of the optic nerves. In case 1, the defect in the left eye was limited primarily to the inferior nasal quadrant of the retina, corresponding to the field defect mentioned, which was compatible with the 6/15 vision. In the right eye failure of development of the retinal ganglion cell layer was more generalized and vision was limited to light perception only. Retinal vessels were present in each eye.

In case 2, determination of the visual fields was impossible because of the age of the patient, but the defect was probably extensive bilaterally, since vision apparently was extremely poor. Light reflexes, however, were preserved, indicating some degree of retinal function.

This anomaly may be differentiated from atrophy of the optic nerve by the unusually small optic disk. In atrophy of the optic nerve in persons who have had normal embryonic development the disk is of normal size or, in extreme cases, only slightly contracted.

#### SUMMARY

Two cases of bilateral congenital hypoplasia of the optic nerve occurring in otherwise normal eyes are reported.

This anomaly is thought to be due to partial failure of development of the ganglion cell layer of the retina and consequent deficiency of neural elements in the optic nerve.

The defect is differentiated from atrophy of the optic nerve.

# News and Notes

EDITED BY DR W L BENEDICT

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## GENERAL NEWS

**Third Pan-American Congress of Ophthalmology.**—The Third Pan-American Congress of Ophthalmology was held in Habana, Cuba, Jan 4 to 10, 1948, inclusive. All who attended felt that the meeting was a great success. Almost 1,400 ophthalmologists were registered, and every country in the Western Hemisphere was represented.

The following officers were elected to serve from 1948 to 1952: President, Dr Conrad Berens, vice presidents, Dr Esteban Adroque (Argentina), Dr Aniceto Solares (Bolivia), Prof Ivo Correa Meyer (Brazil), Dr John MacMillan (Canada), Dr Santiago Barrenechea (Chile), Dr Francisco Vernaza (Colombia), Dr Alexis Aguero (Costa Rica), Dr Miguel Branly (Cuba), Dr Varas Samaniego (Ecuador), Dr Miguel Medrano (Guatemala), Drs Frederick Cordes and William Benedict (United States), secretary for area north of Panama, Dr Thomas D Allen, secretary for area south of Panama, Dr Moacyr E Alvaro, assistant secretaries for Latin America, Dr Jorge Balza and Dr Manoel Silva, assistant secretary for the United States, Dr Brittan F Payne, assistant secretary for Central America, Dr Palomino Dena.

It was decided at the council meeting and ratified by the general assembly that the following permanent committees should be appointed:

**Inter-American Federation of Ophthalmologic Societies.**—President, Dr William Benedict (United States), members: Dr Jorge Malbran (Argentina), Dr Aniceto Solares (Bolivia), Dr Sylvio Abreu Fialho (Brazil), Dr Italo Martini (Chile), Dr Carlos Mena (Costa Rica), Dr Jorge Suarez Hoyos (Colombia).

**Committee on Lighting and Optics**—President, Dr Magin Diez (Argentina), members: Dr J Pascal (United States), Dr Roque Belido Tagle (Peru), Dr J M Penichet (Cuba), Dr Rivas Cherif (Mexico), Dr A Cowan (United States), Dr Caretti (Argentina), Mr Tolman (New York).

**Committee on Glaucoma**—President, Dr Antonio Torres Estrada (Mexico), members: Dr Peter Kronfeld (United States), Dr Julio Raffo (Peru), Dr Hilton Rocha (Brazil), Dr Baudilio Courtis (Argentina), Dr Esteban Adroque (Argentina).

**Committee for the Encouragement of Research in Ophthalmology**—President, Dr Edwin Dunphy (United States), members: Dr Phillips Thygeson (United States), Dr Esteban Adroque (Argentina), Dr Paulo Filho (Brazil), Dr Lech Jr (Brazil).

**Committee on Pharmaceutics**—President, Dr Hughes (Chicago, United States), members Dr Roberto Pereira (Argentina), Dr K Swan (United States), Dr Parker Heath (United States)

**Society of "Amigos"**.—Honorary president, Dr Francisco Belgeri (Argentina), president, Dr Paulo Cesar Pimentel (Brazil), members Dr William Crisp and Dr Shaler Richardson (United States), Dr Magin Diez (Argentina), Dr Santiago Barrenechea (Chile), Dr Abelardo Zertuche (Mexico)

**Committee on Establishment and Guidance of Ophthalmologic Societies**—President, Dr Jesus Rhode (Venezuela), members Dr Frederick Cordes (United States), Dr Durval Prado (Brazil), Dr Roberto Pereira (Argentina), Dr Oscar Horstmann (Cuba)

**Committee on Legal and Industrial Ophthalmology**—President, Dr Jorge Diaz Guerrero (Colombia), members Dr Ralph Lloyd (United States), Dr Alberto Urrets Zavalía (Argentina), Dr Santiago Barrenechea (Chile), Dr J M Espino (Venezuela), Dr Morris Davidson (United States), Dr Jose A Sena (Argentina), Dr Tomas R Yanes (Cuba), Dr Eduardo Arce (Bolivia), Dr Colombo Spinola (Brazil)

**Committee on Standardization of Ophthalmic Hospitals and Clinics**—President, Dr J H Dunnington (United States), members Dr Magin Diet (Argentina), Dr Ivo Correa Meyer (Brazil), Dr J M Penichet (Cuba)

**Committee on Inter-American Medical Relationships**—President, Dr R Pacheco Lua (Guatemala), members Dr Daniel Kirby (United States), Dr Derrick Vail (United States), Dr Palomino Dena (Mexico), Dr Sylvio Abreu Fialho (Brazil), Dr Georgiana Theobald (United States), Dr Olga Ferrer (Cuba)

**Committee of Purchasing Section**—President, Dr Rene Contardo (Chile), members Dr Paiva Goncalves (Brazil), Dr Luis E de Mora (Peru), Dr Jorge Malbran (Argentina), Dr Roberto Vazquez Barriere (Uruguay)

**Contact Lens Center Committee**—President, Dr Baudilio Courtis (Argentina), members Dr Arno Town (United States), Dr Enrique Bertotto (Argentina), Dr Daniel Silva (Mexico), Dr J Pascal (United States)

**Committee on Orthoptics**—President, Dr Avery Prangen (United States), members Dr Jorge Malbran (Argentina), Dr Cesar Rodriguez (Peru), Dr Raimundo Tartari (Argentina), Dr J Mendonca de Barros (Brazil)

**Committee on Scientific Cinematography**—President, Dr Hilton Rocha (Brazil), members Dr Gilberto Cepero (Cuba), Dr A Bedell (United States), Dr Magin Puig Solanes (Mexico), Dr Caretti (Argentina)

**Committee on Trachoma**—President, Prof Cesario de Andrade (Brazil), members Dr Jose R Toja (Argentina), Dr Roque Bellido Tagle (Peru), Dr Paula Santos (Brazil), Dr Phillips Thygeson (United States)

**Bureau of Professors.**—President, Dr Jorge Valdeavellano (Peru), members Dr Derrick Vail (United States), Dr R Rodriguez Barrios (Uruguay), Dr Miguel A Branly (Cuba), Dr Alberto Urrets Zavalia (Argentina).

**Committee for the Prevention of Blindness.**—President, Dr Alberto Vazquez Barriere, members Dr Tomas R Yanes (Cuba), Dr Sanchez Bulnes (Mexico), Dr Natalicio de Farias (Brazil), Dr Magin Diez (Argentina), Dr C Espildora Luque (Chile), Dr Franklin Foote (United States)

**Committee on Statutes**—Dr Tomas R Yanes, Dr Moacyr E Alvaro, Dr Conrad Berens, Dr Alberto Vazquez Barriere, Dr Thomas D Allen, Dr Santiago Barrenechea

**Board of Censors**—President, Dr Tomas R Yanes (Cuba), members Dr Alberto Vazquez Barriere (Uruguay), Dr Esteban Adroque (Argentina), Dr Enrique Cipriani (Peru), Dr Derrick Vail (United States), Dr Rene Contardo (Chile), Dr Paulo C Pimentel (Brazil), Dr Luis Sanchez Bulnes (Mexico), Dr Constantino Herdocia (Costa Rica)

**Committee on Neuro-Ophthalmology**—President, Dr Alejandro Posada (Colombia), members Dr Pedro Falcao (Brazil), Dr Jorge Malbran (Argentina), Dr Esteban Adroque (Argentina) Dr Frank Walsh (United States), Dr Alfred Kestenbaum (United States)



## Obituaries

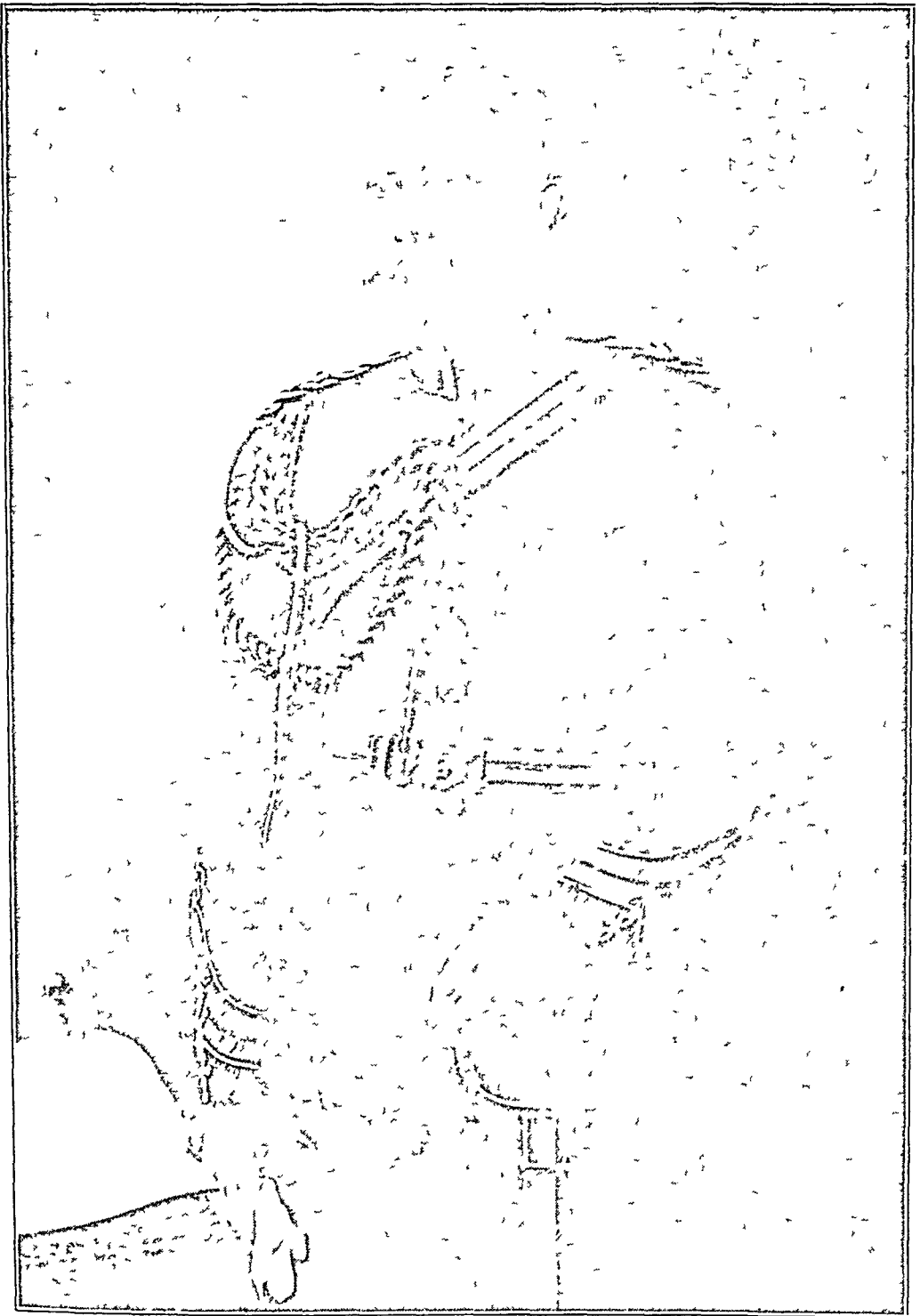
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HENRY SMITH, I M S

1859-1948

Colonel Henry Smith died in his old home and birthplace, Clogher, Tyrone County, Ireland, on Feb 28, 1848. He received his education at Queen's College, Galway, and, after graduating from the Royal University of Ireland with first honors, entered the Indian Medical Service in 1890. Dr. Smith served thirty years in the Punjab, principally in Julundur and Amritsar, and in 1910 rose to the rank of Lieutenant Colonel, Chief Medical Officer of the province, Companion of the Indian Empire and Honorary Surgeon to the Viceroy. The extent of the daily activities which fell to the lot of a medical member of the Indian Medical Service was measured by his varied duties, he was in charge of the civic hospital and superintendent of the jail, was prepared to do autopsies and served as member of the plague commission and as supervisor and attendant of outlying health dispensaries. The work in general surgery was most varied, ranging from litholopaxy to excision of the superior maxilla, and in the Punjab there were many persons with cataract. The patients with cataract came to the hospital during a period of six weeks in the spring and again in the late fall, as governed by the climatic conditions. While the average yearly number of cataract operations in the hospitals in this province was usually about 300, in the hospital under Colonel Smith's management this number rose to 2,000 or 3,000 a year, so that during the cataract season 50 to 100 cataract operations were performed every day. With this enormous material, it is easily understood that a progressive surgeon soon found the old type of operation unsatisfactory, principally because of the resulting reactions from retained capsule and cortex and the frequent necessity for secondary operation. As the inadvertent, spontaneous intracapsular extraction gave such unexpectedly good results, Colonel Smith, following the work of Drs. MacNamara and Molroney, revived the intracapsular extraction, with the most important addition of control of the orbicularis muscle. Gradually, with his remarkable acumen and courage, he developed and publicized the intracapsular cataract operation which in a modified form has become the accepted procedure of the present day.

A man of large stature, Colonel Smith was a fearless operator. With deft and sensitive fingers and a studied appreciation of the delicacy of



the anatomic structure of the eye, he applied pressure in his cataract operation with exact direction and control, so that the returning vitreous pressure ruptured the suspensory ligament according to the laws of hydrostatics

He wrote many articles describing his method and a book which is a classic (*Treatment of Cataract*, Calcutta and London, Butterworth & Co, 1928), with illustrations by the late Dr D T Vail, of Cincinnati. Besides the men of India, many surgeons from England, Europe and America visited the Colonel for inspiration and instruction, and found serious and generous welcome and encouragement.

After his retirement in 1921, he returned to India in 1925-1926, for one season, to devise a modification of his operation, which is fully described in a second edition of his textbook, and with which he believed all criticism which had sprung up was answered.

In 1898 Colonel Smith married Hester Dill Russell, a physician, also in the Indian Medical Service, they had two sons.

A man of original and independent thought, he often approached a problem in a way different from long-accepted methods and thereby aroused criticism. He was so thoroughly convinced of the correctness of his reasoning and so fervidly defended it that his strong personality frequently led to disputes and altercations in the press and at meetings, where he demonstrated a characteristically determined pugnacity. Any opposition to the intracapsular method aroused his fighting instincts, which perhaps often obscured the real issue.

Colonel Smith was a dominant personality who, by his faithful work, made a great name for himself in India and added to the prestige of that remarkable institution, the Indian Medical Service, which contributed so greatly to the distinction of the British rule. In ophthalmology he will always be remembered for his pioneer work in the development of the intracapsular operation.

ARNOLD KNAPP

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Col W F Harvey, now of Edinburgh, has forwarded these reminiscences. "I first came in contact with Major Henry Smith in 1902, when, as Deputy Sanitary Commissioner of the Punjab I was deputed to examine plague vaccine bacteriologically. He invited me to stay with him in Jullundur. I can say, truthfully, that it was an honor conferred on a junior officer by a great man, for he was indeed a great man, not only in mind but in body.

"He was a general, as well as an ophthalmic, surgeon. At his operations, in a small theater, the bazaar population would frequently be gazing in at the window. Over the tables a stoneware jar filled with dilute red mercuric iodide (1:3,000) hung from the roof, from which a small rubber

tubing could supply a continuous stream to the field of operation Smith was a true follower of Lister, and his operations were successful It was his habit also to smoke a cigar through the operation 'If I have to lay down my cheroot, Harvey,' he said, 'it is a bad operation, and if my cheroot goes out, it is a damned bad operation' No doubt the curiosity of sightseers turned many such jesting remarks into actual happenings

"Many incidents and discussions dimly recur to my memory of those days when I lived with Dr Smith in the Chhota Bari Dari, a bungalow belonging to the Maharaja of Kapurthala Smith, for instance, at that time had little belief in the mosquito theory of malaria He remembered being on service in the Bolan Pass and how, with unturned earth in the digging of trenches, epidemic malaria broke out among the troops His views on night blindness and its successful treatment were, if I remember rightly, sound, and his argumentation was both logical and forcible In his early days I think he had set out to be a lawyer By the time I knew him he was not only logical but legal and, like most Irishmen, 'agin the Government' His pet aversion was the government of India's attempt to regulate the amount of fees payable by patients for successful operation Smith's name is linked just as firmly and rigidly to extraction of the lens in the capsule as Freyer's name is linked to the operation on the prostate Colonel Smith was not the inventor of the intracapsular operation for cataract, nor did he claim to be, it is not too much to say that he developed and publicized the operation

"A memorable occasion was the great Jonathan Hutchinson's visit to India to study leprosy He stayed with the Colonel Naturally, he was an enthusiastic admirer The Colonel collected a goodly number of patients for his benefit, 40 cases that morning Dr Hutchinson, no longer young, became tired, so Dr Smith told me to accompany him back to the bungalow On the way, I said, 'Well, sir, what do you think of that operation?' In reply, he said 'Well, I don't think I should recommend a beginner to start on it in preference to the old one, but if I were advising a young man who wanted to specialize either in cataract or in bladder surgery, I should advise him to come here to study' "

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Dr C B Meding writes "In an Indian bungalow, in a room 20 by 20 feet, about whose wall, except for a door and a window about 4 feet from the floor, ran a desklike shelf, on which lay, in order, an open volume of the 'Encyclopaedia Britannica,' an atlas and a dictionary, there stood the man I had traveled 10,000 miles to see, Col Henry Smith, I M S He turned to greet me, held out his great hand and said, smilingly, 'How much do you know about physiological optics?' I answered wisely, 'Nothing' From that moment, until his death, I was, with many another, his pupil We found example, instruction and guid-

ance under a tireless, kindly enthusiast. He presented ophthalmology with a jewel of surgery and lived to see its acceptance. 'Of such is the kingdom of medicine'."

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Col C H Reinhold published the following note in the *British Medical Journal* (1 912 [May 8] 1948)

Not enough has been made in the short obituary notice in the *Journal* of April 17 (p 765) of the pioneer work that Col Henry Smith did in cataract surgery during the early years of the century, and the violent controversy which raged up and down India in ophthalmic circles in those days over extraction of the cataractous lens in its capsule. The operation is still widely practiced in India (or was, when I left there ten years ago), and in capable hands is continuing to give good results. Many surgeons from Europe and America came to sit at his feet and carried his technique and teaching back to their own countries. But his was not a one-track mind and his originality extended into other fields of medicine. When I and my contemporaries were being taught in the medical schools of the U.K. at the turn of the century to treat shock with stimulants and were pumping strychnine into our patients, he was already advocating morphine. He was a great man and ahead of his time as a thinker. I feel that I must pay this tribute to his memory as one who fell under his spell in Jullundur nearly forty years ago.

The following note is taken from the *Indian Pioneer*, the leading newspaper in India.

Colonel Smith has left India. Men may come and men may go, but men of the calibre of Colonel Smith do not come and go every day. It is unnecessary to comment on his world fame as an ophthalmic surgeon. He gave the world better, surer and safer eye sight. He had pupils from every land at his Jullundur and Amritsar clinics. Many who on arrival were skeptical of the numbers of ophthalmic and general surgical operations performed, carried home the story of their astonishment and admiration of a brilliant surgeon and a great man. All noted the rigidity of his ethical life, right was right and no number of wrongs made a right, truth was truth and no casuistry made falsehood into truth. He was plain, blunt, open and above board with everybody from sweeper to prince. His skill and kindness brought him into close contact with India's people. They named him Jullundur Smith and so he was known in every Indian village. No white man knew the people of the Punjab better, he loved them and they reciprocated. He was a great influence in the maintenance of the British raj. He was big, mentally, morally and physically and he operated on thousands upon thousands for two great Indian afflictions, cataract and stone. India mourns his going, the world honors him.

## Abstracts From Current Literature

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### Biochemistry

ON THE PRESENCE OF HISTAMINE IN THE AQUEOUS HUMOUR NILS EMMELIN and ERIK PALM, *Acta ophth* **22** 117, 1944

The authors give experimental data showing that in the aqueous of dogs, cats, rabbits and oxen a substance has been detected that causes contraction of guinea pig intestine. This substance resembles histamine in the following ways. The muscular contraction caused by aqueous resembles that caused by histamine. Aqueous produces bronchial constriction in the guinea pig. The substance is destroyed by boiling in alkaline, but not in acid, solution.

An increase in the histamine content of the blood plasma by intravenous injection of histamine does not increase the histamine content of the aqueous.

O P PERKINS

### Conjunctiva

ALLERGIC CONJUNCTIVITIS AND KERATITIS A MAGITOT, *Ann d'ocul* **178** 321 (Aug) 1945

The author states that the clinician sees many cases of conjunctivitis and keratitis in which the etiologic agent is neither a bacterium nor a virus. These conditions are considered inflammatory for lack of a better definition. The term allergy, however, connotes something different, and the purpose of the paper is to point out the significant differences.

The author's consideration of allergy, immunity and hypersensitivity is followed by a classification of the different types of allergy that occur. He discusses the allergic responses that occur in the ocular tissues, such as the immune-allergic reaction which can be produced in the cornea of experimental animals.

This discussion is followed by a description of allergic conjunctivitis. The acute form is characterized by pronounced edema and dilatation of the conjunctival vessels, and the subacute form by follicles, moderate edema and an eczematous lesion of the skin, such as one sees associated with the sensitivity to atropine. The third form consists essentially of hypertrophy of the conjunctival follicles. The allergic reaction seen in staphylococcal and streptococcal conjunctivitis is described.

Phlyctenular keratoconjunctivitis is discussed at length in the final section of the paper, and the various etiologic factors are considered. The author expressed the belief that phlyctenular keratoconjunctivitis in children is related to tuberculosis, but this does not signify that the lesion itself is tuberculosis. In adults the same type of lesion may occur but in most cases must be attributed to a different allergen.

P ROBB McDONALD

## Cornea and Sclera

THE INFLUENCE OF GENERAL METABOLIC AND NUTRITIONAL DISTURBANCES UPON THE RESISTANCE OF THE CORNEA A FUCHS *Am J Ophth* **30** 721 (June) 1947

Fuchs remarks the strength and resistance of the cornea and discusses the following conditions which cause lowered corneal vitality lagophthalmos, cerebral hemorrhage, marantic corneal ulcers, keratomalacia, exophthalmic goiter and eczematous conjunctivitis He believes that the basic condition in these is a striking diminution of the vitality of the connective tissue apparatus

W S REESE

THREE CASES OF INJURY OF THE LENS WITHOUT DEVELOPMENT OF CATARACTS N DISLER, *Vestnik oftal*, 1946, vol 25

A boy, aged 15, had a bilateral injury of the lenses with fragments of glass from an exploded test tube The right lens became opaque within seven to ten days and was extracted The glass fragment in the left lens was surrounded by the injured anterior capsule of the lens Within a year the capsule around the foreign body became thicker, but the opacities of the lens adjacent to the site of the injury cleared and vision was 0.9 with a normal size pupil and 0.3 with the pupil dilated This patient was observed for seven years Most likely the foreign body firmly surrounded by the capsule of the lens closed up the hole in the lens without allowing the aqueous to penetrate the lens and produce a traumatic cataract Since the eye remained quiet for seven years with good vision, there was no indication for surgical intervention

In the second patient, the lens was injured with a small copper foreign body at 10 o'clock near the limbus The lens became opaque along the route of the injury, and calcinosis developed Vision remained 0.4 during one and one-half years of observation The foreign body was floating freely in the vitreous

The third patient, a young physician, had a small, transparent foreign body in the upper and inner part of the posterior capsule of the left eye There was a small opacity in the anterior capsule with a firm synechia with the iris at the site of entrance The eye was quiet during three years of observation

Disler discusses the prognosis of traumatic cataract according to the changes observed with focal illumination and slit lamp (appearance of vacuoles) and the indications and contraindications to the removal of foreign bodies in the lens

O SILCHEVSKA

TRANSPLANTATION OF AN ENTIRE CORNEA P RIISE, *Acta ophth* **21** 26, 1944

This is a case report of transplantation of an entire cornea to an eye wherein the cornea had sloughed out as a result of ulceration After a year, the central and temporal parts of the implant were sufficiently clear to allow observation of the pupil Vision was limited to hand movements

O P PERKINS

## Experimental Pathology

LOCAL TREATMENT OF INTRABULBAR INFECTIONS II THE CLINICAL AND HISTOLOGICAL PICTURE OF THE STAPHYLOCOCCUS INFECTION  
G RONNE, *Acta ophth* **22** 105, 1944

The results of experimental injection of staphylococci into rabbit eyes are described. With the strain selected, a dose of 50 bacteria injected into the vitreous was sufficient to produce perforation of the eye in less than four days. The infection was characterized by considerable edema of the cornea, pronounced congestion and exophthalmos. These signs were all present on the second day. If the injection is made in the anterior chamber, there is intense iritis with hypopyon, together with early infiltration, ulceration and necrosis of the cornea. In most cases, however, the course is somewhat less malignant, and larger doses of organisms (ten to one hundred times as great) are required.

In the case of infection in the vitreous, the histologic picture is characterized by primary reaction on the part of the retina and ciliary body—changes occurring in the choroid only when this barrier has been broken down. Iris and anterior chamber remain intact and free from bacteria for a relatively long time.

O P PERKINS

## General

MEDICAL ASSISTANCE AT PROFESSIONAL LEVEL P HEATH, *Am J Ophth* **30** 992 (Aug) 1947

Heath concludes that the development of a professional group of ophthalmic associates will contribute substantially to medical care for ophthalmologic conditions. He suggests a program that can be created within existing educational facilities.

W S REESE

## General Diseases

AMAUROSIS ASSOCIATED WITH PERFORATED AND BLEEDING DUODENAL ULCER D FORGARASI, *Wien klin Wchnschr*, **58** 716 (Nov 29) 1946

Forgarasi observed blindness in a man aged 49 with bleeding and perforated duodenal ulcer. The patient had had gastric disturbances almost constantly since 1940. Blindness following loss of blood had received little attention in the surgical literature, but in the ophthalmologic literature a considerable number of such cases are reported. In men, usually in the fourth and fifth decades of life, it is generally hemorrhage in the gastrointestinal tract that is responsible for this form of blindness. In women, however, this form of amaurosis is usually observed after profuse loss of blood incident to childbirth or abortion. Amaurosis has been observed also after venesection. The degree of visual disturbance varies, but loss of vision is usually complete. For treatment blood transfusions have been recommended, but liver and iron preparations, as well as acetylcholine and strychnine, have been used. The prognosis is usually unfavorable.

J A M A, W ZENTMAYER



PRESENT DAY CONCEPTION OF THE DEVELOPMENT OF INTRAOCULAR TUBERCULOSIS A SAMOILOV, *Vestnik oftal* 25 3, 1946

Samoilov, an authority on intraocular tuberculosis, analyzes the previous concept of the etiology of intraocular tuberculosis, the literature, the experimental work done in this field and his vast clinical material

The first problem was that of establishing the site of the primary tuberculosis lesion. A careful roentgenographic examination of 300 patients with metastatic tuberculosis of the eye showed that in only 15 per cent of the patients was active tuberculosis present in the lungs or in the bronchial glands. However, in many other so-called healthy persons the roentgenographic examination showed old scars in the parenchyma of the lungs and bronchial glands, evidently, the tuberculous process in these patients was of mild form and passed under the disguise of grip or influenza. During such a period the virulent tubercle bacilli might invade the blood stream. The special anatomicophysiologic relation which exists in the uveal tract makes the choroid a favorable site for the hematogenous bacterial influx. Samoilov compares the choroid to a basin, in which the greatly slowed down blood current flowing through the innumerable vascular labyrinths of the choroid favors the settling of the particles of the blood, thus, he explains why the primary intraocular tuberculosis lesion is located invariably in the uveal tract, from which the bacilli may be transmitted to the retina, the sclera or the cornea. This view was also maintained by Aexfeld, Stock and Siegrist.

The tubercle bacilli carried to the uveal tract may be latent for a long time, or they may produce a mild lesion, which also may remain latent for a prolonged period, but when the general and local immunity is weakened, the slightest provocation—mild disease of the eye or trauma—may result in a flare-up of the latent tuberculous lesion in the uvea. The interval between the appearance of the initial latent lesion in the uveal tract, or the presence of the bacilli in the blood stream, and the active process in the uvea may be several years, and this fact explains why it is almost impossible to obtain a culture of tubercle bacilli from the blood in cases of a severe tuberculous lesion in the eye. The lesion in the eye usually does not become activated until the intrathoracic lesion is entirely quiescent, explaining the rarity of simultaneous ocular and pulmonary tuberculosis, only in rare cases of low general immunity are the ocular lesions combined with pulmonary tuberculosis.

The role of the general immunobiologic condition of the organism in the etiology of metastatic tuberculosis of the uvea was shown by the experimental work of Kaminsky and Yusefova in Samoilov's clinic, and the observations of these authors were of aid in the diagnostic problem. If there is an active tuberculous lesion in the lungs with simultaneous severe uveitis, the uveitis could be considered of tuberculous origin only when the Mantoux reaction is negative, i.e., when the general immunity of the organism is greatly lowered. When the Mantoux reaction is positive, the tuberculous character of the uveitis can be eliminated.

The relation of the immunity of the organism and the activation of the ocular metastatic lesions led to the creation of a whole series of reliable, safe diagnostic tests with tuberculin, as well as to a bolder use of tuberculin therapy. If the lesion in the uveal tract is the only tuber-

culous lesion in the organism, large therapeutic doses can be applied, with the expectation of obtaining a localized reaction to each dose, and thus making the therapy effective

OLGA SITCHEVSKA

RETINITIS CENTRALIS SEROSA (MASUDA'S DISEASE) S STENSTROM,  
Acta ophth **21** 97, 1944

The literature concerning this condition is briefly reviewed, and 5 cases of his own are submitted. None of them throws light on the question of etiology, but the author regards it as likely that a circulatory disturbance is the cause of the characteristic macular edema.

O P PERKINS

POLYARTHRITIS URETHRITICA SIMPLEX WITH OCULAR SYMPTOMS (REITER-FREUND SYNDROME) H SKYDSGAARD, Acta ophth **21** 107, 1944

Four cases of the syndrome described by Reiter in 1916 are reported. The syndrome consists in purulent urethritis, purulent conjunctivitis and multiple swellings of the joints, the exact sequence of involvement being variable.

The etiologic factor is unknown, but it is definitely not gonorrheal.

O P PERKINS

### **Glaucoma**

PRIMARY GLAUCOMA AND THE PITUITARY-DIENCEPHALIC SYSTEM H ZONDEK and G WOLFSOHN, Am J Ophth **30** 569 (May) 1947

Zondek and Wolfsohn found changes pointing to the pituitary-diencephalic system in 16 out of 22 cases of glaucoma, 6 of these presenting pituitary tumors. They suggest that the term "pituitary-diencephalic" glaucoma be used for such cases.

W S REESE

PATHOGENESIS OF GLAUCOMA M MARIN AMAT, Arch Soc oftal hispano-am **6** 1012 (Oct) 1946

After an extensive discussion of the factors and mechanisms involved in the production of primary glaucoma, the author comes to the following conclusions:

- 1 The ocular hypertension which is the cardinal symptom of glaucoma is the result of an increase in the blood and lymph supply of the eyeball.
- 2 If this increase takes place suddenly, acute glaucoma occurs, if slowly, chronic glaucoma is the result.
- 3 The regulatory center for the intraocular circulation is dependent on the neurovegetative system and is represented by the small ganglions located in the ciliary body and in the choroid, which act under the control of the autonomic nervous system.
- 4 Disturbances in this center produce disturbances in the sympathetic-parasympathetic equilibrium, which regulates the amount of blood flowing in and out of the eyeball.
- 5 As a consequence of this disturbance of equilibrium dilatation of the blood vessels, stagnation in the circulation, increase in the permeability of the capillary endothelium

and hypertension occur 6 The causative factor in the alteration of this equilibrium is a primary excitation of the sympathetic nervous system, which brings about an initial and persistent excitation of the parasympathetic nervous system 7 Therefore, the pathogenesis of glaucoma is predominantly a parasympathetic hypertonic reaction or at times exclusively a parasympathetic action

On the basis of these statements, Marín Amat draws the following clinical conclusions 1 The prophylactic treatment of glaucoma should be directed toward avoiding any condition which may bring about excitation of the neurovegetative system, and the "curative" treatment should endeavor to weaken the action of the nerve plexuses in the ciliary body and at the root of the iris 2 The surgical treatment of glaucoma should be directed against the production of intraocular liquids, and not against their elimination 3 The existence of nerve ganglions in the root of the iris, in the ciliary body and in the choroid, acting autonomically, explains the failure of the surgical procedures performed on the sympathetic nerve or its ganglions to lower the intraocular tension It is necessary to act not on the nerves but on the eye—in the root of the iris and in the ciliary body, as here the regulatory center of the intraocular circulation is located

H F CARRASQUILLO

GLAUCOMA—VASCULAR NECROSIS—EXPULSIVE HEMORRHAGE W A MANSCHOT, *Acta ophth* 23 309, 1945

An anatomic description is given of 6 eyes in which an expulsive hemorrhage occurred after extraction of the lens In 5 of these eyes a severe form of glaucoma was present In 5 of the 6 eyes, necrosis of the posterior ciliary arteries appeared to be the direct cause of the hemorrhage It is probable that glaucoma can cause vascular necrosis, especially in the posterior ciliary arteries Further study of a great number of glaucomatous eyes is necessary to confirm this suspicion

O P PERKINS

### Hygiene, Sociology, Education and History

TEACHING OF OPHTHALMOLOGY IN THE UNITED STATES G QUEIROGA, *Arq brasil de oftal*, 8 75 (June) 1945

Queiroga, who held a Pan-American Congress of Ophthalmology—Kellogg Foundation fellowship from October 1943 to December 1944, describes the methods of teaching ophthalmology in the United States throughout the medical course He also gives a short report of his work during the year of his fellowship at the University of Iowa

M E ALVARO

### Injuries

EXTENSIVE TRAUMATIC IRIDODIALYSIS WITH REPAIR F W NEWELL, *Am J Ophth* 30 695 (June) 1947

Newell reports the case of a 24 year old soldier who sustained a traumatic iridodialysis extending from 10 to 7 o'clock in the left eye

nasally A successful cosmetic result was obtained by incarcerating shreds of iris in a corneoscleral wound A brief discussion of this type of surgery is appended

W S REESE

THE REGENERATION OF WOUNDS OF EXTERNAL MEMBRANE OF THE EYE IN THE LIGHT OF NEW PATHOLOGICO-ANATOMICAL RESULTS  
E T LEVKOIEVA, Brit J Ophth 31 336 (June) 1947

The subject is considered under the following heads clinical and anatomic approach to perforating wounds of the eye, a review of the methods of closing ocular wounds, the regenerative process of the external membranes of the eye, and classification of eye injuries

Levkoieva reaches the following conclusions The regeneration of the sclera and cornea is not the ordinary granulation process of connective tissue, proceeding by the fibrovascular way, with its peculiar cycle of development of the cellular elements, but a proliferation *sui generis* of similar cellular forms that morphologically are near to tissue cultures The dynamics of this process are characterized by an extraordinary intensity, as a result of which—in unfavorable conditions—is seen a surplus growth, chiefly as a result of the penetration of the regenerative tissue in the liquid milieu of the eye

Following the described peculiarities of this process and the idea that the eye, as a closed chamber, is ideally adapted for tissue cultures in vitro, one should use the experience of histologists and their ability to regulate the growth of the tissue elements

Clinical and experimental research of the best methods of closure of wounds of the eye should be undertaken and also of the regulation of the regenerative process of the healing of the wound, besides seeking surgical perfection, one should treat this procedure as analogous to tissue culture

In connection with surplus regeneration of the wound of the eye is seen an autonomous fibromatosis in the eye, pathologically a different form of disease, that has nothing in common with sympathetic ophthalmia, but is clinically similar to it With present knowledge, it is still included under the common diagnosis of traumatic iridocyclitis It should be differentiated from this disease in the future

W ZENTMAYER

### Lens

ENDOCRINE CATARACT REPORT OF CASES M L GUILLAUMAT, Bull Soc d'opht de Paris, (Nov-Dec ) 1946, p 86

Guillaumat describes 5 patients with cataract which he believes is of endocrine origin He bases his classification on the facts that the age at which such cataract occurs is usually between 40 and 50, that the lesion is under the posterior capsule, that arterial tension is normal or below, that contractures occur in these patients similar to those found in patients with tetany, and that eighth nerve impairment is present A study of the family tree reveals antecedents with cataracts The calcium content of the blood is rarely modified Finally, by using parathyroid

hormone with vitamin D and calcium, only 1 of the 5 patients gave any sign that therapy was of value

L L MAYER

### Neurology

HYPERTONIC PARALYSIS OF GAZE J DEREUX, *Ann d'ocul* 178 199 (May) 1945

The author reports 2 cases of chronic (Huntington's) chorea associated with paralysis of all voluntary ocular movements. The first case, that of a woman aged 32, was characterized by all the neurologic signs and symptoms of progressive chorea. The eyes could not voluntarily be moved in any direction. Following movements were likewise absent. Convergence was accomplished with difficulty. When the patient was told to look to the right, the eyes remained immobile, but she turned her head to the right. Once the head was turned, further conjugate movement to the right was possible. If the head was fixed so that it could not be turned to the right, the eyes remained immobile.

There was no other evidence of nuclear paralysis. The results of ocular examination were otherwise normal. After the injection of 0.25 mg of scopolamine hydrobromide, her gait became freer, and voluntary conjugate ocular movements were present in all directions. The second case was exactly similar, but the patient did not receive an injection of scopolamine.

The author states that he knows of no other reported cases that are exactly like his. The loss of voluntary movement with preservation of reflex movements is unusual. The ocular movements that were carried out, i.e., the conjugate movements possible when the head was turned to one side, were slow and jerky, as though the eyes had to overcome some resistance. Alajouanine was the first to describe a somewhat similar condition, and he expressed the belief that the condition was caused by hypertonicity of the muscles. Schaeffer took exception to this interpretation, since the Parkinson syndrome is due to a lesion of the extrapyramidal tract and is characterized by preservation of voluntary movements but loss of automatic movements. Unless the ocular muscles are an exception to this, he does not see how the findings can be explained on the basis of muscle tonus. Pierre von Morax stated that the syndrome of hypertonicity might be a modification of voluntary paralysis of gaze. He mentioned the negative response to scopolamine in Alajouanine's case.

The author concludes that there are two types of paralysis of gaze, the true paralysis and the hypertonic paralysis. He bases this statement on three presumptive signs: (1) the slowness of the ocular movements, (2) the accompanying signs of a lesion of the extrapyramidal tract and (3) the possible occurrence of the voluntary paralysis in all directions of gaze. The unequivocal sign is the disappearance of the paralysis following the injection of scopolamine.

P ROBB McDONALD, M D

## Ocular Muscles

DUANE'S SYNDROME J SERPA, *Rev brasil oftal* 4 43 (Sept) 1945

A case of Duane's syndrome is reported in detail Serpa places Duane's syndrome with Austregesilo Filho's neurodysplasia (1943), a "generic designation of an alteration in the embryogenesis of the nervous system, encephalic or medullary"

M E ALVARO

SQUINTING POSITION OF WEAK-SIGHTED EYES P BROENDSTRUP, *Acta ophth* 22 386, 1944

The author has examined the nature of the ocular deviation assumed by the weak eye in a series of 162 persons affected with monocular cataract or aphakia. The patients are divided into three groups. Group 1 comprised 32 cases in which the cataract was congenital. Here divergence was found in 50 per cent and convergence in 40 per cent. Group 2 comprised 70 cases in which the cataract was acquired before the tenth year of life. Here divergence was found in 74 per cent and convergence in 13 per cent. Group 3 comprised 60 cases in which the eye became affected at the age of 11 or later. Here divergence was found in 67 per cent and convergence in 12 per cent.

O P PERKINS

## Operations

REPAIR OF FACIAL DEFECTS BY LOW-NECK PEDICLE FLAPS ROBERT H IVY, *Plastic & Reconstruct Surg* 1 117, 1946

Cutaneous and subcutaneous tissue from the lower part of the neck is devoid of hair and is similar to that of the face in texture and color. The scar from its removal is usually inconspicuous and can be readily concealed. Pedicles from the neck may safely cross the midline, which refutes the dictum that a pedicle should never cross that line. Jerome Webster, T G Blocker and the author have had good results with pedicles from the lower part of the neck. Convincing photographs support these successes.

L P GUY

MULTIPLE EXCISION AND Z PLASTICS IN SURFACE RECONSTRUCTION FERRIS SMITH, *Plastic & Reconstruct Surg* 1 170, 1946

A new use of the Z plastic procedure combined with multiple excision of undesirable tissue is emphasized as the method of choice for restoring to normal deformities caused by burns, keloids, scars and congenital lesions but not if the tissue is malignant. This method reduces consequent distortion of the eyelids, nose and angle of the mouth and ears. A more desirable cosmetic result is obtained than with transplanted skin flaps and grafts. The method is not useful in the upper infraorbital area of the male because of the introduction of hair-bearing skin.

L P GUY

## Orbit, Eyeball and Accessory Sinuses

UNILATERAL EXOPHTHALMOS, AN EARLY SIGN IN THYROTOXICOSIS W  
H KISNER and H MAHORNER, Surg, Gynec & Obst **84** 326  
(March) 1947

Kisner and Mahorner report 5 cases of unilateral exophthalmos due to toxic diffuse goiter. In all of these cases the unilateral exophthalmos was a prominent sign, and in some it was the only one noticed by the patient. The cause of exophthalmos is not established, but from experimental studies it would appear that a factor in the secretion from the anterior lobe of the pituitary has the property of producing exophthalmos, and the same or a different factor has the property of inducing hyperplasia of the thyroid gland. The erroneous impression exists that the exophthalmos immediately subsides following thyroidectomy, but even in cases with high basal metabolic rates the exophthalmos is frequently a little worse in the weeks immediately after the operation. Only after many weeks and months does the exophthalmos gradually subside. Because of the long time over which improvement in exophthalmos after thyroidectomy may occur, radical procedures, such as the Naffziger operation, should be deferred unless extreme proptosis greatly jeopardizes the sight of the eye.

J A M A, W ZENTMAYER

PANOPHTHALMITIS IN A PREMATURE INFANT TREATED BY STREPTOMYCIN  
L B SOMERVILLE-LARGE, Brit J Ophth **31** 362 (June) 1947

A case of panophthalmitis in a premature child following infection of the umbilical cord by *Bacillus proteus* is described. The initial treatment consisted in the administration of sulfadiazine by mouth and penicillin by injection. During the first six days of this treatment the ocular condition became steadily worse. Streptomycin was then substituted, and although the lid and orbital condition improved, on the ninth day of the beginning of this treatment the globe perforated and evisceration was performed. The author considers the streptomycin to have overcome the inflammation of the uveal tissue, as prior to the commencement of treatment with streptomycin *B. proteus* was found in pure culture in the anterior chamber, but after treatment the cultures from the highly infected globe were negative.

W ZENTMAYER

## Physiology

RATE OF DARK ADAPTATION AND REGIONAL THRESHOLD GRADIENT OF  
THE DARK-ADAPTED EYE. PHYSIOLOGIC AND CLINICAL STUDIES L L  
SLOAN, Am J Ophth **30** 705 (June) 1947

Sloan studied 9 patients, in addition to normal persons, whose elevated light thresholds were restored to normal by vitamin therapy. The findings indicate that riboflavin, in addition to vitamin A, may be required to effect complete recovery. These studies suggest that concentric contraction of the visual field occurs frequently in patients with ocular vitamin A deficiency and probably indicates cone as well as rod involvement.

W S REESE

THE NUMBER OF QUANTUMS NECESSARY FOR THE PERCEPTION OF LIGHT BY THE HUMAN EYE H A VAN DER VELDEN, *Ophthalmologia* **111** 321 (June) 1946

The author criticizes previous work done on the influence of the quantum character of light on vision at low levels of illumination. He considers that too little emphasis has been placed on the statistical character of the light quanta when determining the number of quanta necessary for a light stimulus. A method is described for the determination of the number of absorbed quanta in the visual purple necessary for the perception of light under conditions of dim illumination. An analysis is then made of the statistics on the observation of light flashes, and the theoretic relationships and the experimental data were compared. Assuming that  $k$  light quanta are necessary for the perception of light, the author found that two such quanta fit all the experimental curves. He considers that it is probable that the cooperation between the two quanta takes place in the nervous system, a concept which is in accordance with other concepts in neurophysiology.

F H ADLER

### Refraction and Accommodation

CONTACT LENSES IN EXCELSIS A H BRIGGS, *Brit J Ophth* **31** 304 (May) 1947

A man aged 22 had been rejected for service in the Civil Air Guard because of myopia. Contact lenses were successfully fitted, and he was then passed without their presence being suspected. The lenses were not detected at two subsequent medical board examinations, in America and on his return to England. He served in the bomber squadron over Germany. Subsequently, he served as a captain of transport aircraft. He entered the service in 1940 and was discharged Jan 1, 1947. He was decorated for courage, determination and devotion to duty. Briggs suggests that the visual acuity regulations for the service ought to be revised to show to what extent contact lenses will be permitted. He asks how far it is justifiable to aid and abet a patient in procuring contact lenses, knowing they are likely to be used to defraud a medical examiner, and how far such a subterfuge is unfair.

W ZENTMAYER

FUKALA OPERATION FOR HIGH MYOPIA C PESCATORI, *Rassegna ital d'ottal* **13** 49, 1946

The author reports on some cases of high myopia in which the clear lens was extracted. The method of operation consisted of a dissection with secondary suction of the opaque lens. No complication except 1 case of glaucoma was met. The only disadvantage is the necessity of repeating the operation when suction of the lens substance is not complete. The improvement of visual acuity is constant. The preferable time for intervention is between the ages of 8 and 20. The grade of myopia best suited is about 20 D. The postoperative astigmatism amounted to 2 D. Changes in the fundus do not constitute a real contraindication, as long as they do not reduce the vision to less than 20/200.

G B BIETTI—J J LOPRESTI



## Retina and Optic Nerve

### RECENT OBSERVATIONS ON THE PATHOGENESIS OF DIABETIC RETINOSIS F NASTRI, *Boll d'Ocul* **19** 24, 1945

Investigations were directed primarily toward showing the behavior of the lipids, vitamin K, vitamin A, carotene and prothrombin in the blood of diabetic persons presenting retinal lesions

The results obtained revealed that in patients with diabetic retinosis there was a definite increase in the blood lipids, hypervitaminosis A and K and an increase of carotene, as well as a relative reduction in prothrombin

The author interprets these findings as an expression of altered hepatic function in patients presenting the picture of diabetic retinosis

G BIETTI—J J LO-PRESTI

### PRELIMINARY ATTEMPTS AT THE SURGICAL TREATMENT OF COATS'S DISEASE A RUBINO, *Riv di oftal* **1** 285, 1946

On the assumption that the primary cause of Coats's disease resides in vascular changes in the choroid, the author treated 2 patients with diathermy coagulation of the choroid through the sclera, with the idea of obliterating and coagulating vessels and arresting the changes occurring in their walls, much as increased permeability and ectasia. The procedure is completed with one or more perforating punctures to permit escape of the subretinal fluid. The results obtained are promising

G B BIETTI—J J LO-PRESTI

### RETINAL DETACHMENT, PREGNANCY AND ECTOPIA LENTIS V VENTOLA and F IRIBARREN, *Arch oftal de Buenos Aires* **21** 232 (Aug) 1946

The patient came to the authors in the sixth month of pregnancy. Ten days before the examination sudden decrease of vision was noted in the right eye. Vision was equal to perception of hand movements. There was congenital bilateral ectopia lentis. The retina of the left eye was normal, no signs of retinitis gravidarum being noted. In the right eye a slightly elevated retinal detachment in the temporal area was observed, no tear being visible. Two problems then had to be solved: the possible relation between the retinal detachment and the pregnancy, and the advisability of operation. As retinal detachment is a frequent complication of ectopia lentis and the prognosis is not very good, and as further examinations showed no tear, rest in bed and a nontoxic diet were ordered. If, about a month after the confinement, a cure has not been effected, an operation will be performed.

M E ALVARO

### RETINAL EDEMA IN TUBERCULOUS DISEASE OF THE ANTERIOR SEGMENT OF THE EYE A SAMOILOV, *Vestnik oftal* **26** 20, 1946

The anterior segment of the eye is frequently involved in metastatic tuberculosis of the eye. The precipitates on Descemet's membrane and opacities of the vitreous in tuberculosis of the uveal tract, however, do

not correspond to the frequently observed marked decrease of visual acuity Samoilov believes that the tuberculous process spreads from the anterior parts of the eye to the posterior segment of the uveal tract and causes an edema of the retina and this explains the reduction of vision at the moment of activation of the tuberculous lesion in the anterior segment of the uveal tract The enlargement of the blindspot, when examined with the campimeter, confirms the fact that edema of the retina is present

Samoilov experimented on an eye with sarcoma of the choroid in the following manner Campimetry revealed no enlargement of the blindspot, the vision in the quiet eye was 20/20 A paracentesis was done, and 0.4 cc of the aqueous was withdrawn The eye became inflamed (ciliary infection), and the campimeter showed a scotoma two hours after the puncture of the anterior chamber Twenty-seven hours after the slight trauma the eye, which was quiet again, was enucleated Pathologic examination did not reveal edema of the retina or changes in the choroid, except the sarcoma and a small detachment of the retina adjacent to the site of the tumor of the choroid This transitory edema of the retina in response to the irritation of the iris and ciliary body, produced by slight trauma, without involvement of the choroid, indicates that retinal edema regularly appears in an active process of the anterior segment of the eye

In a number of cases of anterior uveitis examination by the campimeter invariably revealed an enlargement of the blindspot, particularly if there was a responsive reaction to treatment with tuberculin Case histories illustrate the point of the author

Samoilov comes to the following conclusions

The most sensitive tuberculin-campimetric test can be used not only for choroiditis but also when there is any other localization of the tuberculous lesion in the eye

The decrease of vision observed in isolated severe tuberculous uveitis is caused by retinal edema as a reaction to the inflammatory process in the anterior segment of the eye

The use of calcium iontophoresis in tuberculosis of the uvea acts not only as a desensitizing factor but also as a valuable therapeutic agent by decreasing the retinal edema and thus increasing the visual function

Further observations will show whether the retinal edema appears specifically in tuberculous lesions of the eye or whether it can be present in lesions of the eye with different cause

OLGA SITCHEVSKA

INVESTIGATIONS ON THE INFLUENCE OF K AVITAMINOSIS ON THE OCCURRENCE OF RETINAL HEMORRHAGES IN THE NEWBORN H WILLE, *Acta ophth* 22 261, 1944

In a control series of 594 newborn infants, the incidence of retinal hemorrhage was 42.4 per cent In the children of mothers who had received intramuscular injections of a preparation of vitamin K at the commencement of labor, the incidence of retinal hemorrhage was reduced to 32.9 per cent

O P PERKINS

## Trachoma

CONTEMPORARY STATE OF TREATMENT OF TRACHOMA A. MURZIN, *Vestnik oftal* 26 25, 1947

A review of the literature on the etiology and treatment of trachoma and the clinical experience of the Kazan experimental trachomatous institute are given. The enthusiasm of the ophthalmologists for the Noguchi gram-negative bacillus and the rickettsia as the etiologic factors of trachoma has abated, and the role of the Prowazek-Halberstadter bodies as the cause of trachoma is being reconsidered.

Scrofulosis, tuberculosis, syphilis, avitaminosis and allergy have an important bearing on the course of the trachomatous process and on the local treatment. Trachoma is a chronic proliferative inflammation, and the treatment must conform to the various clinical stages of the disease.

The mechanical therapeutic measures are widely used in the United Soviet Socialist Republics in the form of repeated expressions of the follicles with local treatment of the conjunctiva in the intervals. The expression acts not only as a mechanical but also as a stimulating or irritating factor, by mobilizing the cellular elements for the control of the infection. Expression therapy is most effective in trachoma in the first and second stages or the granular stage of the disease, and is applied frequently in young adults and children. However, it is contraindicated in cases with a secondary infection of the conjunctival sac, and in allergic irritation of the conjunctiva, as it may cause an exacerbation of the process and cause a corneal ulcer.

The experience of the Kazan Institute is that sulfonamide therapy, both local and general, is of positive value, mainly in corneal involvement and in secondary conjunctival infection. The action of the sulfonamide compounds on the trachomatous changes is rather slow, although it causes a gradual absorption of the infiltrates and follicles. Murzin, therefore, considers it advisable to combine sulfonamide therapy with expressions of the follicles. The sulfonamide compounds are most effective in the first and second stages of trachoma. A study is being made of the combined treatment of trachoma with sulfonamide compounds, taken orally, and autohematotherapy.

The newer antibiotics—penicillin, gramicidin and aspergillin—act most effectively in secondary infections in trachoma.

In children the local application of sulfonamide compounds gives best results.

Diathermocoagulation has been used in the Kazan Institute since 1941 in cases of resistant, long-standing trachoma, in 3 of which the disease did not respond to routine treatment. In 53 cases, the third therapeutic stage of trachoma was changed into the fourth stage within twenty-two to thirty-two days.

Tissue therapy after Filatov's method has not influenced the course of trachoma.

OLGA SITCHEVSKA

## SOCIETY TRANSACTIONS

Edited by Dr W L Benedict

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*Sixteenth Annual Meeting, San Francisco, July 2, 1946*

### **Cytologic Character of Conjunctival Exudates.** DR PHILLIPS THYGESON, San Jose, Calif

In a microscopic study of smears of exudate and conjunctival scrapings in 2,000 cases of conjunctivitis of diverse origin, variations in leukocytic reactions and epithelial changes were observed to be sufficiently pronounced to have diagnostic value

Polymorphonuclear cell exudates were characteristic of bacterial infections in general, but there were a few exceptions Morax-Axenfeld conjunctivitis was characterized by a fibrinous exudate without leukocytes unless there was a secondary staphylococcic infection Chronic conjunctivitis due to *Neisseria catarrhalis* also showed a minimal or no leukocytic reaction

Conjunctivitis produced by the typical viruses always showed a characteristic mononuclear cell exudate with few, if any, polymorphonuclear cells In contrast, the three viruses of the psittacosis-lymphogranuloma venereum group of viruses, those of trachoma, inclusion blennorrhea and lymphogranuloma venereum, always showed a polymorphonuclear cell exudate

Epithelial changes consisting of various degrees of keratinization were of value in the diagnosis of early vitamin A deficiency Mild keratinization of the epithelium combined with an increase in goblet cells and mucus was characteristic of keratoconjunctivitis sicca

A predominance of eosinophils in the exudate was characteristic of vernal conjunctivitis and of typical conjunctival allergies, such as conjunctivitis associated with hay fever With bacterial allergy, as exemplified by phlyctenular conjunctivitis, eosinophils were not present in the exudate A conjunctival basophilia was also observed with the typical allergies but was neither so constant nor so specific as the eosinophilia The occurrence of free eosinophilic and basophilic granules released from disintegrating cells was found to have diagnostic value

The expressed follicular contents of the cells of trachoma and that of other follicular conjunctivitis showed striking differences in cytologic character These differences appeared to be related to the cellular necrosis which is a striking feature of trachoma but not of the other diseases

In only a few exceptional instances were the cytologic changes observed in this study pathognomonic of the etiologic type of conjunctivitis concerned, but when correlated with clinical and bacteriologic findings they were often of diagnostic importance

#### DISCUSSION

DR JAMES H ALLEN, Iowa City Can a distinction be made between acute conjunctivitis, Beal type, and epidemic keratoconjunctivitis on the basis of cytologic differences?

DR PHILLIPS THYGESON, San Jose, Calif I think that no distinction can be made at present between the cytologic changes in these two diseases It was thought at one time that specific inclusion bodies were associated with epidemic conjunctivitis, that is, bluish, amorphous bodies in the cytoplasm of conjunctival and epithelial cells of the cornea which had some diagnostic significance, but these same bodies have since been observed with other diseases, and it is thought that they are nonspecific

DR JAMES H ALLEN, Iowa City Do you consider macrophages (Leber cells) pathognomonic of trachoma?

DR PHILLIPS THYGESON, San Jose, Calif The Leber cell is nothing but a large macrophage Such cells were observed with trachoma and were certainly more numerous than with any other type of conjunctivitis studied, but they were also noted with other infections It seems to me that the presence of numerous Leber cells in association with signs of cell necrosis and a predominance of lymphoblasts does indeed make a pathognomonic picture I believe that macrophages in other types of conjunctivitis tend to be definitely smaller than the Leber cell, which is an extraordinarily large macrophage

I am sure that the cells stem from the same source, but there is an extraordinary difference in size between macrophages in cases of trachoma and those associated with other types of conjunctivitis

DR JAMES H ALLEN, Iowa City Will you discuss the importance of a proper selection of the site for removal of material for cytologic study?

DR PHILLIPS THYGESON, San Jose, Calif It is a good rule to take cytologic material from the point of maximum intensity of the disease In cases in which smears of exudate are taken, this is not of much significance, since most exudate accumulates in the inner canthus Scrapings, however, are best taken from the site of maximum intensity of the disease

When one is looking for evidence of suspected vitamin A deficiency, it is important to recognize that the temporal portion of the limbus is the site most commonly affected in the early stages One should, then, take scrapings from the area of the outer temporal portion of the limbus This is the site where a Bitot spot is most commonly seen

DR DONALD J LYLE, Cincinnati What are the best stains to use routinely in the laboratory investigation?

DR PHILLIPS THYGESON, San Jose, Calif I have used a half-dozen cytologic stains, and I prefer the Giemsa stain The material is fixed in absolute methyl alcohol and then stained in dilute Giemsa so-

lution (1 drop to 2 cc of neutral distilled water) for about an hour. The slide is then passed through two changes of 95 per cent alcohol to remove the debris of the stain. This method results in a very satisfactory cytologic stain. Then, there is the Wright stain, which is satisfactory and is more rapid. I am sure there are two or three other stains which would work equally well, but I, personally, prefer the Giemsa stain.

DR V C RAMBO, Mungeli, Central Provinces, India. Will Dr Thygeson discuss the differentiation of inclusion blennorrhea and trachoma?

DR PHILLIPS THYGESON, San Jose, Calif. I think it is possible to make a cytologic differentiation between these two diseases, especially in the adult. Both diseases have identical inclusion bodies, both diseases are characterized by a polymorphonuclear cell exudate. It is the cytologic picture of the follicles which makes the differentiation possible. In inclusion conjunctivitis in the adult, the follicles show none of the degenerative changes characteristic of trachoma, and one gets the cytologic picture of the nontrachomatous follicle, in contrast to the numerous cytologic changes so characteristic of trachoma.

I recognize that clinical differentiation is possible in most cases, but there are certainly occasional confusing cases in which cytologic study may be of value.

DR K W ASCHER, Cincinnati. Did you observe, in cases of vitamin A deficiency, syncytium-like membranes of keratinized epithelial cells?

DR PHILLIPS THYGESON, San Jose, Calif. I may have seen such changes, but I did not recognize them as particularly characteristic. I am sorry, I really cannot answer that question.

DR EDWARD C ELLETT, Memphis, Tenn. In speaking of the reaction to atropine, Dr Thygeson made the distinction that the reaction to atropine was an allergic one and that to physostigmine a toxic one. Did he make any tests for sensitivity to these two drugs on patients with these conditions?

DR PHILLIPS THYGESON, San Jose, Calif. First, I noted that there was a striking clinical difference between the types of conjunctivitis produced by these two drugs. The reaction to atropine was typically a contact conjunctivitis and dermatitis, with widespread dermatitis of the eyelids, whereas I never saw cutaneous reactions produced by physostigmine. I recognize that they may well occur, but I have not seen them personally. Second, I noted that the conjunctival reaction in atropine conjunctivitis was a papillary hypertrophy, whereas in physostigmine conjunctivitis it was a follicular hypertrophy.

I made a number of tests, both patch and intradermal, and I was consistently able to obtain a positive reaction to the patch test for atropine. Some were low grade and others rather violent. However, I never succeeded in obtaining a reaction to the patch test for physostigmine. I did not make serologic studies.

**Macular Edema.** DR ARTHUR J BEDELL, Albany, N Y.

The common causes of edema of the macular region were demonstrated.

Special attention was drawn to Berlin's edema, the various causes of holes at the macula and the inflammatory reactions of retinochoroiditis and retinitis

Since in hemorrhagic exudate and traumatic hole it is probable that there is always edema at some time, cases of each were included

Preretinal and retinal edema were explained as a pushing outward of the vitreous, producing the ring-shaped light reflex which is on it

Some of the recent papers on macular edema were referred to, and additional illustrations of juvenile macular degeneration, central serous retinopathy, local detachment of the retina and foveomacular diseases were presented

*Conclusions*—Edema of the macular region may be the isolated expression of either a local or a general tissue reaction. The edema may be limited to and disappear from the macula, or it may be the precursor of extensive retinochoroiditis or a gross macular change. The healed macula may show pigmented specks, white dots, heaped-up pigment, atrophy or thick scars, which may be smooth and flat or rough and nodular

This paper was illustrated by a series of "kodachrome" photographs

#### **Experimental Dinitrophenol Cataract** DR J W BETTMAN, San Francisco

Dinitrophenol was estimated by Horner to be associated with the development of cataract in obese persons in an incidence of 0.86 per cent. It was associated with the development of cataract in obese mice in an incidence of 75 per cent. The cataract has often occurred in human subjects after the withdrawal of dinitrophenol therapy, it did not occur in obese mice after the withdrawal of dinitrophenol. It did not occur in ordinary, nonobese mice in any circumstances

Dinitrophenol caused lenticular opacities in fowl within eight hours after a diet containing dinitrophenol was instituted. The opacities cleared spontaneously while the fowl were still on the diet. In comparable doses, dinitrophenol failed to cause opacities of the lens in young or adult obese mice whether or not they were subjected to higher temperatures

The direct injection of dinitrophenol into the anterior chamber of chickens and rabbits caused lenticular opacities in each species within approximately one-half hour. The opacities cleared within twenty-four hours. Rabbits did not acquire opacities of the lens when fed dinitrophenol. The direct immersion of the lenses of chickens, obese mice and rabbits into a solution of dinitrophenol did not produce opacity in a comparable length of time

*Conclusions*—The results of these experiments led to the following conclusions and conjectures

- 1 Dinitrophenol acts only on the lens *in vivo* of mammalian and avian species

- 2 The lens *in vitro* does not show this opacity. This may be due to one of several factors: (a) Dinitrophenol, when in the anterior chamber, forms another compound, which then acts on the lens. (b) The permeability of the lens capsule is different when the lens is *in vitro*

than when it is in its normal state (c) Dinitrophenol interferes with a phase of metabolism of the living lens, such as production of an increased need for oxygen or the formation of more lactic acid

3 The failure of the transient opacities observed in fowl to develop in mammals is due to a difference in metabolism of the species, and not to a difference in the lenses themselves

4 The significance of differences in metabolism is confirmed by the occasional occurrence of permanent cataracts in congenitally obese mice. Such opacities did not occur in nonobese mice. This frequency of cataract formation is comparable to the incidence of cataract in obese persons and may explain the previous failures of numerous investigations to produce cataract in experimental mammals

5 The difference in incidence of cataract in fowl and in mammals is apparently not due to the difference in body temperature. The age of the animal is little, if at all, related

Numerous questions related to dinitrophenol cataract remain unanswered. Is the cataract-producing action of dinitrophenol due to its effect on oxidation or on sugar metabolism or to something else? Why does the cataract which develops so rapidly in a chick clear spontaneously while the chick is still receiving the same concentration of dinitrophenol? Why did cataract occur with great rapidity in human subjects months after the ingestion of dinitrophenol had been discontinued?

Work is being continued in an attempt to answer some of these vexing problems

#### DISCUSSION

DR CLYDE A. CLAPP, Baltimore. I should like to ask in how many of the male subjects dinitrophenol cataract developed. Are there any reports in the literature?

What was the difference as seen with the slit lamp between the co-called reversible opacities in the birds and the permanent opacities in the mice?

DR J. W. BETTMAN, San Francisco. Dinitrophenol cataract has been reported in human male subjects in 1 or 2 instances. I have forgotten the precise number of cases in the literature. They are not common, but they have been reported.

The picture of the reversible cataract in the chick seen with the slit lamp was that of a dense opacity entirely limited to the subcapsular layers of the lens. The remainder of the lens was not involved at any stage.

In the permanent opacities in the mice, the first observable change was the same type of subcapsular opacity, posterior at first and then anterior, in association with the development of the anterior opacity, or at about that stage, the nucleus begins to get a bit milky, and an opacity then develops in the entire lens.

DR CONRAD BERENS, New York. Are dinitrophenol and dinitrocresol synonymous terms? A clinician in New York claimed that there is a difference, but in 2 obese women who were treated with dinitrocresol cataracts developed rapidly. One was 28 and the other 60 years of age.

DR J. W. BETTMAN, San Francisco. The terms dinitrophenol and dinitrocresol are not synonymous, but the drugs act, so far as is known, in precisely the same manner. Clinically, dinitrophenol has been used



largely in the United States, and dinitrocresol in Europe. They both produce cataract, and so far as I know, they both act in the same manner. The group of drugs to which they belong is usually designated as the "dinitro bodies," because the substances are so similar in their action.

### **Changes in the Angioscotomas Associated with the Oral Administration of Hexobarbital Soluble** DR. AUSTIN I. FINK

For some time ophthalmologists have been concerned with the question whether barbiturates are contraindicated in treatment of patients with glaucoma. This concern has derived to a great extent from the observation that large doses of barbiturates have produced dilatation and have increased the permeability of the cerebral blood vessels and the capillary bed.

Angioscotometry was chosen as a suitable method for this experiment, since changes in the normal angioscotoma are assumed to represent alterations in the function of the retinal perivascular space.

The scotoma was mapped according to the method advocated by Evans. The defects in the visual fields could thus be studied both qualitatively and quantitatively.

Studies were carried out on 10 subjects, 9 women and 1 man. The ages of the subjects ranged from 21 to 26 years. All known causes of alteration of the angioscotoma were carefully eliminated. Each subject was in good health.

On a controlled series of 5 of the subjects an experiment was carried out in which capsules containing 4 grains of lactose (0.26 Gm.) were administered orally. The subjects did not know that the capsules contained merely a placebo. The purpose of the control study was to ascertain whether a psychologic factor was present and was a factor in causing the alterations in the angioscotomas occurring after the ingestion of hexobarbital sodium. The method, technic and procedure employed were identical with those used for the studies of hexobarbital. The results demonstrated that in the series of 5 subjects no alteration in the angioscotoma was recognizable.

The oral administration of 4 grains (0.26 Gm.) of hexobarbital sodium was associated with widening of the angioscotoma in 8 of 10 subjects. In the other 2 subjects no recognizable change was shown.

Administration of a placebo containing 4 grains of lactose to 5 of the subjects of the hexobarbital series produced no alteration in the angioscotoma.

One might ascribe the associated effect of hexobarbital sodium on the normal angioscotoma to changes in (a) the functions of retinal perivascular space, (b) conductivity of the retinal neurons and synaptic junctions and (c) the parasympathetic nervous system.

### **Relation of Maternal Vitamin A Intake, Level of Vitamin A in the Maternal Blood and Ocular Abnormalities in the Offspring of the Rat** DR. BLANCHE JACKSON and DR. V. EVERETT KINSEY, Boston

In accordance with technics devised by Warkany and Schraffenberger, a series of 57 weanling female rats were grown to maturity

without the accumulation of hepatic stores of vitamin A. They were then bred and given only minimal amounts of vitamin A during pregnancy. Four of the mothers carried their fetuses to advanced stages of development. The eyes of the young in these litters showed the abnormalities which have been described by Warkany and Schraffenberger.

To determine the limiting level of the dose of vitamin A for female rats producing young with abnormal eyes, similarly prepared female rats were given 2, 3, 5 or 10 U S P units of vitamin A daily. They were then bred, and the supplementary administration of the vitamin was continued at the same level. Young obtained from mothers fed less than 3 to 5 U S P units daily showed the ocular defects already mentioned, whereas all those receiving more than this amount of the vitamin had normal eyes, even though in many cases the dose of vitamin A was insufficient for normal delivery.

Values for vitamin A of the serum taken during pregnancy from female rats producing young with abnormal eyes were found to be less than 12 U S P units per hundred cubic centimeters in every instance (normal, 75 U S P units per hundred cubic centimeters). The addition of 100 U S P units of vitamin A daily or the feeding of a stock ration after the fifteenth day of pregnancy, with or without treatment with penicillin or sulfathiazole, did not reduce the high percentage of fetal resorption observed in the previous experiments.

It is concluded that ocular defects occur in the young rat only when the maternal vitamin A deficiency is extremely severe, so advanced, in fact, that fetal resorption is common and normal birth is impossible.

To the extent that the physiologic processes associated with reproduction in human beings parallel those in the rat, it may be inferred that vitamin A deficiency in the mother is not a probable cause of retrolental fibroplasia.

#### DISCUSSION

DR CONRAD BERENS, New York. This study is a piece of research which is vital to the prevention of blindness. About 51 per cent of blindness in the schools for the blind is due to congenital abnormalities.

DR DERRICK VAIL, Chicago. Were any skeletal malformations observed, especially in the optic foramen or at the base of the skull?

DR V EVERETT KINSEY, Boston. We have not yet examined the eyes of the animals for other defects, including skeletal abnormalities, so I am unable to answer that question. Warkany, I believe, has described such defects in detail.

DR DERRICK VAIL, Chicago. I wish to sound a note of warning here. A few weeks ago, I testified in a criminal court case brought against a specialist in quack vitamin therapy who cited experimental work, reported in Iowa, on vitamin D deficiency as a cause of anophthalmos in a litter of newborn pigs. In his pamphlets broadcast widely to the public, he used the reports of these experiments to terrify pregnant women and urged them to buy his vitamin product as a prevention of blindness in the unborn child.

I should like to have a firm statement to the effect that the results of your experiments are not yet applicable to human beings.

DR V EVERETT KINSEY, Boston I think our conclusion was to the effect that, in so far as the physiologic processes were the same in rats and in human beings, vitamin A deficiency is not a probable cause of retrolental fibroplasia

Even though we have to change our minds, I think that, for the record, it might be well to be overcautious and to say definitely that these results do not suggest that maternal vitamin A deficiency is in any way associated with ocular abnormalities in infants

DR T L TERRY, Boston It is not intended to detract from this presentation, but I think it would interest you to know that pediatricians working on the problem of retrolental fibroplasia found clinically that this abnormality, which Jackson and Kinsey have reproduced, has developed in 2 infants whose vitamin A in the blood level was kept normal by therapeutic measures It may interest you further that, according to Clifford and Allers, vitamin A, when dissolved in oil, is not absorbed by the premature infant from the gastrointestinal tract, nor is it absorbed after subcutaneous or intramuscular injection These authors found that when the vitamin A is dissolved in glycerol instead of oil the level of the vitamin in the blood was elevated In 2 infants who had received such injections, retrolental fibroplasia developed despite normal vitamin A levels in the blood

### **Role of the Lens Substance in Experimental Gonorrheal Iritis**

DR MAURICE J DRELL, MISS MARJORIE BOHNHOFF and

DR C PHILLIP MILLER, Chicago

In the course of studies on experimental gonorrheal iritis in rabbits, it was noted that the infection was serever and more likely to become chronic in eyes in which the lens had been traumatized at the time of inoculation The present study was undertaken in an effort to explain this observation and to evaluate the role played by the lens substance in the experimental infection

The inoculation of gonococci into the anterior chamber of the rabbit with injury to the lens resulted in a moderately severe and chronic inflammatory reaction The inoculation of gonococci without injury to the lens produced a mild inflammatory reaction Inoculation of a gonococcus-lens mixture without injury to the lens usually caused a similar reaction The injection of lens substance without injury to the lens or the injection of isotonic solution of sodium chloride with injury to the lens produced only an insignificant inflammatory response Lens substance *in vitro*, particularly after autolysis, prolonged the survival time of gonococci No clear evidence of mulitiplication was obtained under these conditions

### **DISCUSSION**

DR JAMES H ALLEN, Iowa City What was the time interval between injection of lens substance in series 5 and the second inoculation of some of the eyes with injury of the lens?

DR MAURICE J DRELL Chicago Five days, by which time the reaction from the injection of lens substance had cleared completely

DR M J HOGAN, San Francisco Do you think lens substance merely exerts a protective effect on the organisms rather than acting as a culture medium?

DR MAURICE J DRELL, Chicago That question bothered us for a long time Dr Miller had been working with the gonococcus for many years, and the project originally was undertaken at the request of the Office of Scientific Research and Development in an effort to produce an experimental infection against which the value of the sulfonamide drugs and other therapeutic agents could be assayed Theoretically, the gonococcus ought to grow in the presence of lens substance We tried to make it grow but were unable to obtain any clearcut evidence of its growth We do know that lens substance is an excellent buffer, the suspension in which lens was present varied only slight from a  $p_H$  of 7.4 to one of 7.2 over a period of five days, whereas the  $p_H$  of gonococcus suspension alone, in saline or in Ringer's solution, became acid, dropping from 7.4 to 6.8 This is probably one of the essential factors However, the lens also contains a great many of the nutritive elements on which the gonococcus should be able to live and multiply, and we were unable to demonstrate any multiplication

The survival time of the individual gonococcus was estimated by Morax to be between three and nine days, the period varying with the strain The survival time of the gonococcus in our study was eight days Whether there was any multiplication during this period we are unable to say positively

DR V EVERETT KINSEY, Boston Were culture mediums containing glutathione or other sulfhydrydes tried?

DR MAURICE J DRELL, Chicago The culture medium used was casein digest-cystine agar, prepared in the laboratory It contained 0.065 per cent cystine, which I believe is a sulfhydryde

DR V EVERETT KINSEY, Boston Cystine or cysteine?

DR MAURICE J DRELL, Chicago Cystine This medium was used for the recovery of the organisms from infected eyes The lens itself contains cystine, which is one of the reasons we thought that the gonococcus should be able to grow on it

DR WALTER B LANCASTER, Boston Will the essayists tell us whether injury to the lens or other optical injury occurs if the gonococci are introduced intravenously or somewhere outside the eye?

DR MAURICE J DRELL, Chicago I presume the question refers to work similar to that reported by Dr Rosenau with streptococci I cannot recall any such investigations with gonococci with positive results

Perhaps a word should be added here The attempt to produce the gonorrheal iritis is nothing new It has been tried almost since the time that the organism was first described The organism apparently needs to have its virulence enhanced in some way The strain used by us was initially enhanced by something like one hundred and thirty-four passages through the mouse peritoneum before it was sufficiently virulent for the purposes of producing this iritis

**Electroencephalography and Ophthalmology** DR ALSTON CALLAHAN, Jackson, Miss, and DR FREDERICK C REDLICH, Boston

Electroencephalography is the technic of recording the electrical beat of the brain In 1902 and 1907, Hans Berger, father of modern

electroencephalography, recorded spontaneous rhythmic fluctuations in the electrical potentials from the brain of animals, and in 1930 he was successful in recording evidence of the electrical activity of the human brain. He showed that normally the beat of the brain appears as a mixture of more or less sinusoidal fluctuation in voltage with a frequency of from 1 to 60 waves per second and that the most commonly recorded rhythm in normal adults has a frequency of approximately 10 per second. Berger proved that this electrical rhythm came from the cortex, and he called the record the electroencephalogram.

The electroencephalogram records electrical activity of the brain from the surface of the scalp, just as the electrocardiogram records that of the heart from the thoracic wall. Like the electrocardiogram, the maximum diagnostic and prognostic value of the electroencephalogram is attained when it is combined with other types of clinical and laboratory examinations.

Electroencephalography has become useful in neurologic diagnosis and has found widespread application. Its greatest usefulness lies in the following fields: (1) the diagnosis of convulsive disorders, (2) the diagnosis and prognosis of head injuries, particularly those accompanied with convulsive seizures, (3) the diagnosis and localization of expanding intracranial lesions, such as tumors, subdural hematoma and cerebral abscess, (4) the diagnosis of narcolepsy, of some types of encephalitis and of the sequelae of meningitis, and (5) the diagnosis of diffuse, inflammatory or degenerative conditions of the brain and of some organic psychoses, and eventually, perhaps, in the diagnosis of personality disorders.

Several problems are of primary interest to ophthalmologists: (1) the local electrical discharges following opening and closing of the eyes and ocular movements, (2) the effect of visual stimulation and opening and closing of the eyes on the occipital electroencephalogram, (3) the diagnosis of false (hysterical or malingered) blindness and (4) the localization of cerebral lesions with visual defects.

Electroencephalography has the following applications in ophthalmology:

- 1 The electroencephalogram is used to record changes in electrical potentials of the eye after ocular movements. These potentials can be observed only when the retina is present, and they are thought to be due to the chorioretinal difference in potential.

- 2 Observations on the effect of visual stimulation and the opening and closing of the eyes were inconclusive. In a series of 100 patients, a statistical scatter of findings resulted. In a series of 30 patients with normal brain waves, opening and closing the eyes in the dark had an effect on the normal occipital rhythm similar to that of the visual stimulus in the dark. The normal occipital wave in man can be driven by repetitive photic stimulation of the retina. No characteristic effect was discovered in 10 cases of amblyopia.

- 3 The effect on the normal occipital rhythm of opening the eyes does not differentiate true from malingered or hysterical blindness.

- 4 The galvanic cutaneous response to visual stimulation can be used to differentiate true from false blindness.

- 5 The electroencephalogram is an aid in localizing cerebral lesions with visual defects. Superficial lesions, especially tumors, frequently show slow waves.

## DISCUSSION

DR DAVID HARRINGTON, San Francisco Was there any correlation between the electroencephalographic pattern and the congruity of the visual fields in the anteroposterior localization of cerebral lesions?

DR ALSTON CALLAHAN, San Francisco The question refers to the hypothesis that the more posterior the lesion, the more congruent are the field defects, and Dr Harrington wishes to know whether we found evidence to support or to disprove this theory. We did not make a study of our cases with this relationship in mind. Case reported 7 cases of homonymous hemianopsia in which operation revealed a tumor of the optic tract and there was loss of normal occipital rhythm over the occipital cortex.

**Further Observations on Aqueous Veins** DR K W ASCHER, Cincinnati

In 1941, for the first time by means of the biomicroscope, aqueous humor was seen to stream through conjunctival and episcleral veins of the normal human eye. Vessels containing a clear fluid, sometimes mixed with varying amounts of blood, can be found in at least one third of all quiet human eyes with the use of the corneal microscope and slit lamp illumination. With the aid of a 10 diameter magnifying loupe and good oblique illumination, they are detectable in more than 14 per cent of all eyes not injected. Emerging from the limbal meshwork, from the depth of the scleral tissue adjacent to the limbus or from a scleral emissarium, these clear vessels join conjunctival or subconjunctival veins. In the recipient vessel, they produce either a considerable dilution of its blood content or a characteristic pattern of stratification with two, three or more differently colored layers, which run parallel to one another along the wall of the vessel. The colorless vessels were termed aqueous veins. They are biomicroscopically visible pathways connecting Schlemm's canal and the intrascleral meshwork with conjunctival and subconjunctival veins. Not all quiet human eyes show aqueous veins, owing to the fact that aqueous humor, on leaving the canal of Schlemm, may become rapidly and completely mixed with the blood which is contained in the intrascleral meshwork. If, however, clear fluid can reach the episcleral or conjunctival veins without the previous addition of too many red blood cells, an aqueous vein will become visible. Anatomic differences in the outlets of Schlemm's canal are rather definite, and it seems reasonable to assume that an outlet measuring 50 microns in diameter will be more important for the elimination of intraocular fluid than another outlet having only one-tenth this diameter. It is possible that in some normal human eyes a great number of outlets are constantly eliminating aqueous humor, whereas in other eyes only a few outlets, or even only one, may carry the bulk of fluid. In eyes of the latter type, surgical or traumatic severing of one of these main channels may initiate a disastrous increase of intraocular pressure.

The possible role of the aqueous veins in the etiology and classification of glaucoma was discussed. Observations on glaucomatous eyes led to the working hypothesis that a transient or permanent narrowing of the outlets of Schlemm's canal may be connected with the presence,

or even may be responsible for the development, of increased intraocular pressure in certain eyes. Clinical observations and reflection suggest the significance of aqueous veins in the mechanism of compensated glaucoma.

Many ophthalmologists have had difficulty in recognizing the aqueous veins, whereas others have confirmed their occurrence and significance. Photographs of recipient vessels have corroborated the presence of highly diluted blood in these vessels, as well as the influence of drugs on the elimination of intraocular fluid through the aqueous veins.

Protracted observation of the veins surrounding the corneoscleral junction will always reveal that one or more individual channels are continually charged with the elimination of intraocular fluid. Physiologic factors and climatic differences in part concur in their effect and in part exercise opposing influences on aqueous veins. Once located, the particular aqueous vein remains discoverable at its original location after months and years and retains its characteristic qualities. Apparent differences in the incidence of aqueous veins, when searched for with a 10 diameter magnifying loupe at different seasons of the year, are due to differences in the red cell content and to the greater difficulty of recognizing an aqueous vein when there is conjunctival congestion. In eyes blind from tabetic atrophy of the optic nerve, the movement of the fluid streaming in aqueous veins is often slow.

The question whether aqueous veins contain aqueous humor or blood deprived of all, or part, of its red cell has recently been answered by Goldmann. He stated that after intravenous injection of a 10 per cent solution of fluorescein sodium the aqueous veins remained colorless, while the blood running in the recipient vessels, in conjunctival and in subconjunctival veins, showed the greenish yellow hue of the dye. India ink, injected into the anterior chamber of an eye with a uveal sarcoma, appeared in a previously located aqueous vein only, and not in any of the other vessels.

The physiologic and clinical significance of the aqueous veins should be acknowledged. The term "aqueous veins," should be accepted for the biomicroscopically visible part of the pathways, which are charged with elimination of intraocular fluid from the canal of Schlemm via the intrascleral meshwork to the conjunctival, subconjunctival and anterior ciliary veins.

#### DISCUSSION

SIR WILLIAM STEWART DUKE-ELDER, London, England. I should like to ask Dr. Ascher one question. He started off by eliminating the arterial system entirely. Does he agree with Dr. Friedenwald that there are direct aberrant arterial vessels in the canal of Schlemm?

DR. K. W. ASCHER. I do not dare to answer that question, for I do not have any pertinent experience of my own.

From the papers published on this subject, I believe that it is possible that these vessels described by Friedenwald not only are present but also fulfill the physiologic function described, or ascribed to them, by Friedenwald.

## CHANGES IN THE OCULAR FUNDUS ASSOCIATED WITH PHEOCHROMOCYTOMA OF THE ADRENAL GLAND

Report of Three Cases

GORDON M. BRUCE, M.D.  
NEW YORK

**P**HEOCHROMOCYTOMAS are tumors growing from cells of the so-called chromaffin system. They are sometimes referred to as paragangliomas, but Belt and Powell<sup>1</sup> suggested that the former term be used in referring to adrenal growths and the latter to chromaffin tumors of other regions. Chromaffin tissue is present in the adrenal medulla, in the carotid gland, in the organ of Zuckerkandl and in sacrococcygeal and retroperitoneal tissue.

Now, as Raab<sup>2</sup> has shown, the only cells of the adrenal medulla to produce a hormone are the chromaffin cells, or pheochromocytes. They produce epinephrine and related catechols (*o*-dihydroxybenzene), which are similar to epinephrine though not identical with it, but which enhance its effect. According to Cannon,<sup>3</sup> there is no excitation without stimulation, such as exercise, emotion or drugs. Plasma taken during a crisis has been found to have a pressor effect. Paragangliomas can produce hypertension, and MacKeith<sup>4</sup> found that in 9 of 13 cases the offending tumor was in the retroperitoneal tissues.

### PATHOLOGIC CHARACTER

Scholl and his collaborators<sup>5</sup> stated that these tumors are usually benign, but Padis<sup>6</sup> expressed the opinion that a tumor which if left to

From the Institute of Ophthalmology of the Presbyterian Hospital of New York.

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1 Belt, A. E., and Powell, T. O. Clinical Manifestations of Chromaffin Cell Tumors Arising from Adrenal Medulla. Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9-24 (July) 1934.

2 Raab, W. The Pathogenic Significance of Adrenalin and Related Substances in the Heart Muscle, Exper. Med. & Surg. **1**:188 (May) 1943.

3 Cannon, W. B. The Adrenal Medulla, Bull. New York Acad. Med. **16**:3-13 (Jan.) 1940.

4 MacKeith, R. Adrenosympathetic Syndrome. Chromaffin Tissue Tumor with Paroxysmal Hypertension, Brit. Heart J. **6**:1-12 (Jan.) 1944.

5 Scholl, A., and others. Review of Urologic Surgery, Arch. Surg. **48**:325-354 (April) 1944.

(Footnotes continued on next page)



itself may kill the patient cannot be so considered Baumgarten and Cantor<sup>7</sup> considered them benign anatomically, but malignant physiologically However, malignant forms appear and have been reported by Ausbittel and Holtz,<sup>8</sup> Lazarus and Eisenberg,<sup>9</sup> Cahill,<sup>10</sup> McGavack and his collaborators,<sup>11</sup> King,<sup>12</sup> Knabe,<sup>13</sup> Bonnamour and his collaborators<sup>14</sup> and others As Eisenberg and Wallenstein<sup>15</sup> have pointed out, these malignant forms are usually bilateral and are not, as a rule, responsible for increased output of epinephrine, but in the cases of McKenna and Hines,<sup>16</sup> Langeron and Delcour,<sup>17</sup> Schroder<sup>18</sup> and numerous others the malignant growth was associated with hypertension

The pheochromocytoma is usually small, rarely exceeding the size of a walnut Wells and Boman<sup>19</sup> stated that the largest known tumor weighed 1,000 Gm, but they had apparently overlooked Borch-Johnsen's<sup>20</sup> tumor, which weighed just twice as much Most cases

6 Padis, N Paroxysmal Hypertension Caused by Adrenal Tumor, *Clinics* **4** 87-96 (June) 1945

7 Baumgarten, F C, and Cantor, M O Pheochromocytoma Case Report, *Ann Surg* **111** 112-116 (Jan) 1940

8 Ausbittel, F, and Holtz, B Unusual Clinical Aspects of Bilateral Medullary Tumor of Adrenal Gland, *Med Klin* **36** 1016-1020 (Sept. 13) 1940

9 Lazarus, J A, and Eisenberg, A A Paraganglioma of Adrenal Two Cases, *J Urol* **27** 1-26 (Jan) 1932

10 Cahill, G F Hormonal Tumors, *Surgery* **16** 233-265 (Aug) 1944

11 McGavack, T H, Benjamin, J W, Speer, F D, and Klotz, S Malignant Pheochromocytoma of Adrenal Medulla (Paraganglionoma) Report of Case Simulating Carcinoma of Adrenal Cortex with Secondary Adrenal Insufficiency, *J Clin Endocrinol* **2** 332-338 (May) 1942

12 King, E S J Malignant Pheochromocytoma, *J Path & Bact* **34** 447-452 (July) 1931

13 Knabe, E Bilateral Pheochromocytoma of the Adrenal Significance of Epinephrine for Clinical Picture of These Tumors, *Virchows Arch f path Anat* **308**.615-628, 1942

14 Bonnamour, S, Doubrow, and Montegue Pleural Metastasis of Paraganglioma of Adrenal Gland, *Ann d'anat. path* **4** 141-146 (Feb 3) 1927

15 Eisenberg, A A, and Wallenstein, H Pheochromocytoma of Adrenal Medulla (Paraganglioma) Clinicopathologic Study, *Arch Path* **14** 818-836 (Dec) 1932

16 McKenna, C, and Hines, L Paraganglioma of Suprarenal Gland, *J Urol* **34** 93-86 (Aug) 1935

17 Langeron, L, and Delcour, J Relation of Adrenal Tumors to Arterial Hypertension, *Arch d mal du cœur* **21** 13-18 (Jan) 1928

18 Schröder, K Unusual Bilateral Chromaffin Tumors of the Adrenal Gland Case, *Virchows Arch f path Anat* **268**·291-299, 1928

19 Wells, A H, and Boman, P G Clinical and Pathologic Identity of Pheochromocytoma of Adrenal Gland Report of Case, *J A M A* **190** 1176-1180 (Oct. 9) 1937

20 Borch-Johnsen, E Operated Case of Paraganglioma Gland Suprarenal Sm Associated "with the Suprarenal Sympathetic Syndrome," *Acta chir Scandinav* **80** 171-179, 1937

occur in the second, third and fourth decades of life, but there are wide variations Linde's<sup>21</sup> patient was 5 months old, and Eisenberg and Wallenstein<sup>15</sup> found a case of a patient aged 82

Microscopically, the tumor is a recognizable reproduction of the chromaffin cells, and the cytoplasm takes a dark stain The growth has a glandular appearance, due to the tendency of the cells to be arranged around a central lacuna

#### BIOLOGIC ASSAY

Numerous biologic assays of excised pheochromocytoma tissue have been performed. Because the normal content of epinephrine in the blood as estimated by Barr<sup>22</sup> is only 1.10,000,000, direct measurement is technically no easy task, but, through work on cats' denervated irises and rabbits' sympathectomized ears, certain relative values have been obtained According to Kalk,<sup>23</sup> the normal adrenal gland contains 1 to 2 mg of epinephrine per gram of tissue The epinephrine content of pheochromocytoma tissue has been found to vary from 1 mg (Kelly and associates<sup>24</sup>) to 30 or 40 mg per gram (Kalk<sup>23</sup>) A common method of estimation of the epinephrine content is to compare the effect of a known quantity of tumor tissue with that of a known quantity of epinephrine (Brunschwig and associates<sup>25</sup>) Mencher<sup>26</sup> reported that each gram of tumor caused a reaction in the cat's denervated iris equal to 8 mg of epinephrine, and Duncan and his collaborators<sup>27</sup> estimated that the tumor had a pressor activity equal to 210 mg of epinephrine Strombeck and Hedberg<sup>28</sup> found that the epinephrine content of the blood was thirty times the normal between crises and one thousand

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21 Linde, P Unusual Tumor (Pheochromocytoma) in Infant Five Months Old, *Nord med (Hygiea)* **13** 897-898 (March 21) 1942

22 Barr, P Recent Advances in Endocrinology, *J A M A* **105**:1760 (Nov 30) 1937

23 Kalk, H Paroxysmal Hypertension Study of Blood Pressure Crises in Presence of Tumor of Medulla, *Klin Wchnschr* **13** 613-617 (April 28) 1934

24 Kelly, H M , Piper, M C , Wilder, R. M , and Walters, W Paroxysmal Hypertension with Paraganglioma of Right Suprarenal Gland, *Proc. Staff Meet, Mayo Clin* **11**:65-70 (Jan 29) 1936

25 Brunschwig, A , Humphreys, E, and Roome, N Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma of Adrenal Gland, *Surgery* **4** 361-370 (Sept ) 1938

26 Mencher, W H Paroxysmal Hypertension Caused by Pheochromocytoma Adrenalectomy, *J Mt Sinai Hosp* **10** 743-746 (Jan-Feb ) 1944

27 Duncan, L E, Jr , Semans, J H , and Howard, J E Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus Disappearance of Diabetes After Removal of Tumor, *Ann Int Med* **20**:815-821 (May) 1944

28 Strombeck, J P , and Hedberg, T P Tumor of Adrenal Medulla Associated with Paroxysmal Hypertension Report of Case Preoperatively Diagnosed and Cured by Extirpation After Capsular Excision, *Acta chir Scandinav* **82**: 177-189, 1939

times the normal during an attack. Free epinephrine has been found in tumors by most observers, but none could be demonstrated by Biskind and his co-workers.<sup>29</sup> Methods used in assaying the tumors have been described by Brunschwig and his collaborators,<sup>25</sup> Langeion and Lohéac<sup>30</sup> and numerous other authors.

#### HISTORY AND OCCURRENCE

Pheochromocytoma of the adrenal gland was first described by Frankel<sup>31</sup> in 1886. In those days the tumor was usually observed at postmortem examination, and little clinical progress was made for more than thirty years. According to Padis,<sup>6</sup> only 3 cases have been recorded in the Lankenau Hospital in Philadelphia and 3 cases in the Johns Hopkins Hospital, in the last seventy-five years. Kirschbaum and Balkin<sup>32</sup> found 3 in 14,437 consecutive cases in the Cook County Hospital, in Chicago.

Pheochromocytoma was recognized as a clinical entity in 1922 by Labbé and his co-workers<sup>33</sup> and firmly established as such by Vaquez and Donzelot<sup>34</sup> in 1926. The first case in which the diagnosis was made prior to operation was that of Pincoffs<sup>35</sup> in 1929. This tumor was removed surgically by Shipley<sup>36</sup>.

Pheochromocytoma has been considered a rare tumor, but it is being detected with increasing frequency of late. For example, up to 1939 Brunschwig and Humphreys<sup>37</sup> had collected 103 cases. In the next

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29 Biskind, G. R., Meyer, M. A., and Beadner, S. A. Adrenal Medullary Tumor. Pheochromocytoma Cured by Surgical Intervention, Clinical Management, Analysis of All Reported Operated Cases, *J Clin Endocrinol* **1** 113-123 (Feb.) 1941.

30 Langeron, L., and Loheac, P. Amount of Epinephrine in Tumors Removed at Necropsy. Significance in Pathogenesis and Pathogenic Mechanism of Arterial Hypertension, *Presse med* **36** 1153-1155 (Sept 12) 1928.

31 Fränkel, F. Bilateral Adrenal Tumor. Report of a Case, *Virchows Arch f path Anat* **103** 244-263, 1886.

32 Kirschbaum, J. D., and Balkin, R. B. Adrenalin Producing Pheochromocytoma of Adrenal Associated with Hypertension. Report of Three Cases, *Ann Surg* **116** 54-60 (July) 1942.

33 Labbe, M., Tinel, J., and Doumer. Solar Crises and Paroxysmal Hypertension Associated with a Tumor of the Adrenal Gland, *Bull et mem Soc med d hop de Paris* **46** 982-990 (June 23) 1922.

34 Vaquez, H., and Donzelot, E. Crises of Paroxysmal Arterial Hypertension, *Presse méd* **34** 1329-1331 (Oct 23) 1926.

35 Pincoffs, M. C. A Case of Paroxysmal Hypertension Associated with Adrenal Tumor, abstracted, *Tr A Am Physicians* **44** 295-299 (May) 1929.

36 Shipley, A. M. Paroxysmal Hypertension Associated with Tumor of Adrenal Gland, *Ann Surg* **90** 742-749 (Oct) 1929.

37 Brunschwig, A., and Humphreys, E. Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, *J A M A* **115** 355-357 (Aug 3) 1940.

five years, according to the figures of Kvale and his collaborators,<sup>38</sup> 17 had been added. In the last two years about 26 additional cases have appeared in the literature. In fact, more than 16 per cent of all cases have been reported in the last two years. The tumor is probably not becoming commoner, but it is certainly being detected more frequently.

#### SYMPTOMS

First of all, it should be remembered that there may be no symptoms at first, and hypertension may be discovered by accident. Later, symptoms may be produced by excitement, stress, worry, changes in position, pressure on the abdomen or neck, hyperventilation (Mortell and Whittle<sup>39</sup>) or even voluntarily, as in the case reported by Porter and Porter.<sup>40</sup> Sometimes malaise or parasthesias appear as premonitory symptoms. According to MacKeith,<sup>4</sup> all symptoms arise from (a) recurrent paroxysms of generalized hypertension, (b) chronic hypertension with renal and cardiac failure or (c) involvement of the cortex of the adrenal gland (such as Addison's or Cushing's disease).

Hypertension is a constant symptom. It is paroxysmal at first but may be continuous, as pointed out by Cahill,<sup>10</sup> Lukens<sup>41</sup> and others. Sometimes the pressures are very high. In Strickler's<sup>42</sup> case there were readings of 330 systolic and 150 diastolic, but in most cases the pressure is about 200 systolic. The paroxysmal phase is not permanent. As Mencher (in his discussion on the paper by Hyman and Mencher<sup>43</sup>) pointed out, the hypertension soon becomes permanent. A similar observation was recorded by Baumgarten and Cantor<sup>7</sup> and several others. The hypertension may last for days, or even months (Edward<sup>44</sup>), and acute paroxysms may last from several minutes to several days. According to MacKeith,<sup>4</sup> the average duration of an attack is two hours.

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38 Kvale, W. F., Roth, G. M., Claggett, O. T., and Dockerty, M. B. Headache and Paroxysmal Hypertension. Observations Before and After Surgical Removal of Pheochromocytoma, *S. Clin. North America* **24** 922-933 (Aug.) 1944.

39 Mortell, E., and Whittle, J. Pheochromocytoma. Case Report, with Certain Observations on Pathologic Physiology, *J. Clin. Endocrinol.* **5**:396-402 (Nov.) 1945.

40 Porter, M. F., and Porter, M. F., Jr. Report of Case of Paroxysmal Hypertension Cured by Removal of Tumor, *Surg., Gynec. & Obst.* **50** 160-162 (Jan., no. 1 A) 1930.

41 Lukens, F. D. W. Diagnosis and Treatment of Disorders of Adrenal Glands, *M. Clin. North America* **26** 1803-1815 (Nov.) 1942.

42 Strickler, C. W., Jr. Pheochromocytoma. Operative Failure, Case Report, *South Surgeon* **11** 193-200 (March) 1942.

43 Hyman, A., and Mencher, W. H. Pheochromocytoma of Adrenal Gland, *J. Urol.* **49** 755-776 (June) 1943.

44 Edward, D. G. F. Pheochromocytoma of Adrenal Gland and Hypertension, with Details of Case, *J. Path. & Bact.* **45** 391-403 (Sept.) 1937.

Allen's<sup>45</sup> patient was under observation for sixteen years, and in Hamilton's<sup>46</sup> case a ten year recession supervened Thoracic pain of the anginal type is frequent Between attacks the patient may feel well, although hypertension may persist Sometimes this may fall to normal for a while (van Goidsenhoven and Appelmans<sup>47</sup>)

Other symptoms include lacrimation and salivation, hemoptysis (MacKeith<sup>4</sup>), diarrhea (Shipley<sup>86</sup>), pain in the hypochondrium and sweating (Kvale and his collaborators,<sup>88</sup> Crane and his collaborators<sup>48</sup> and Duncan and associates<sup>27</sup>) Van Epps and his co-workers<sup>49</sup> listed, in addition, such symptoms as sensations of fulness and pressure in the neck, pallor followed by flushing, cyanosis of the nail beds, angiospasm of the extremities and the tip of the nose, tachycardia (occasionally bradycardia), forceful cardiac impulse, nervousness, muscular weakness, air hunger, tinnitus, vertigo and nausea

During attacks the urine may be either plentiful or scanty to the point of anuria, albumin and casts may be found According to Vaquez and Donzelot,<sup>34</sup> the latter may be due to small renal hemorrhages produced during the paroxysms Between attacks the urine is normal, until definite renal damage supervenes

Glycosuria and hyperglycemia are reported in a great number of the cases, and the diabetes disappears when the tumor is removed (Duncan and associates,<sup>27</sup> Biskind and his collaborators<sup>29</sup> and others) Sometimes the glucose readings are very high, in Strickler's<sup>42</sup> case, for example, the fasting blood sugar was 283 mg per hundred cubic centimeters That some diabetic patients had been harboring an unsuspected tumor was shown by Duncan and associates,<sup>27</sup> who cited cases of Herde, Kelly, Biebl, Wichsel, Rogers and de Wesselow In all of them the patients had been treated for diabetes, and in all pheochromocytomas were observed at autopsy Other cases of glycosuria were reported by Van Epps and his co-workers<sup>49</sup> (273 mg of glucose

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45 Allen, P L Chromaffin Cell Tumor Associated with Paroxysmal Hypertension, *Texas State J Med* **36** 540-542 (Dec) 1940

46 Hamilton, J E Pheochromocytoma of Adrenal with Paroxysmal Hypertension Case Relieved by Surgery, *Kentucky M J* **38** 572-575 (Dec) 1940

47 van Goidsenhoven, F, and Appelmans, R Paroxysmal Hypertension of Adrenal Medullary Origin Clinical and Therapeutic Study, *Bull Acad roy de med de Belgique* **14** 672-694, 1934

48 Crane, J J, Abson, L A, and Touriel, E L Tumor of Medulla of Adrenal Gland Associated with Paroxysmal Hypertension Case Preoperatively Diagnosed and Cured by Surgical Removal, *J Urol* **46** 1100-1102 (Dec) 1941

49 Van Epps, E F, Hyndman, D R, and Greene, J A Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal Report of a Proved and of a Doubtful Case, *Arch Int Med* **65** 1123-1129 (June) 1940

per hundred cubic centimeters), Landau and associates,<sup>50</sup> Ausbittel and Holz<sup>8</sup> and others

In nondiabetic cases, the blood picture is not greatly affected, but increased lymphocytes were reported by MacKenzie and McEachern,<sup>51</sup> Hatieganu and associates<sup>52</sup> and others

In many cases the basal metabolic rates have been greatly increased, often in association with diabetes. In Strickler's<sup>42</sup> case the basal metabolic rate was +74 per cent, in McCullagh and Engel's,<sup>53</sup> +36 per cent, and in Binger and Craig's,<sup>54</sup> +61 per cent. Other signs of hypermetabolism are not necessarily present. Just as the diagnosis of diabetes mellitus is sometimes made in cases of pheochromocytoma, so are the symptoms occasionally ascribed to hypermetabolism. In fact, in the case reported by Brunschwig and Humphreys<sup>37</sup> an operation had previously been performed for thyrotoxicosis, apparently without deleterious effect. Here, again, successful removal of the adrenal tumor is followed by a fall in the basal metabolic rate. In Hyman and Mencher's<sup>48</sup> case it fell from +69 to -17 per cent, and in Evans and Stewart's<sup>55</sup> case, from +43 and +48 to -13 and -17 per cent, respectively. Similar cases have been reported by Rabin<sup>56</sup> and others.

Since Raab<sup>2</sup> has shown that epinephrine in the blood is absorbed by heart muscle, the electrocardiographic findings are of interest. They have been analyzed by MacKeith.<sup>4</sup> During attacks there were found auricular premature beats, tachycardia, bradycardia, arrhythmia, slurring of the QRS complex, left axis deviation, and inverted, flattened or elevated T waves. Between attacks the electrocardiograms in one third of the cases were normal. Of the others, large P waves were present in 3 cases, but left axis deviation and diminution or inversion of the T waves were usual.

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50 Landau, A., Paszkiewicz, L., Slavinski, Z., and Steffen, E., Jr. Grave Paroxysmal Hypertension in Patient with Paraganglioma of the Adrenal Gland. Clinical Study, with Particular Reference to Diagnosis, *Rev belge sc méd* **8** 330-343 (May) 1936.

51 MacKenzie, D. W., and McEachern, D. Tumor of Adrenal Medulla (Pheochromocytoma), with Removal and Relief of Paroxysmal Hypertension, *J Urol* **40** 467-476 (Oct) 1938.

52 Hatieganu, I., Moga, A., and Radu, P. Changes in Blood Picture (Lymphocytosis) During Hypertensive Crises Due to Paraganglioma of Adrenal Gland, *Zentralbl f inn Med* **61** 337-344 (May 25) 1940.

53 McCullagh, E. P., and Engel, W. J. Pheochromocytoma of the Adrenal Gland with Hypermetabolism. Two Cases, *Ann Surg* **116** 61-75 (July) 1942.

54 Binger, M. W., and Craig, M. M. A Typical Case of Hypertension with Tumor of Adrenal Gland, *Proc Staff Meet, Mayo Clin* **13** 17-20 (Jan 12) 1938.

55 Evans, W. F., and Stewart, H. J. Peripheral Blood Flow in Case of Adrenal Pheochromocytoma Before and After Operation, *Am Heart J* **24** 835-842 (Dec) 1942.

56 Rabin, C. B. Chromaffin Cell Tumor of Suprarenal Medulla (Pheochromocytoma), *Arch Path* **7** 228-243 (Feb) 1929.

Pheochromocytoma of the adrenal gland is so often associated with other pathologic changes that it is difficult to separate the original symptoms from those of accompanying diseases and complications, and other findings are therefore discussed under the head of differential diagnosis. Mortell and Whittle<sup>59</sup> accounted for the wide variations in symptoms by the supposition that the active principle secreted by a pheochromocytoma may not be the same in all cases, a statement which is admittedly conjectural. When death occurred, it was found to have been immediately due to one of many causes, most frequently acute pulmonary edema, shock, cerebral hemorrhage or chronic renal failure. Oberling and Jung's<sup>57</sup> patient died in labor, Hick's<sup>58</sup> had a subarachnoid hemorrhage, and Stevens and Waite's<sup>59</sup> had a ruptured thoracic aorta. Other cases of rapid or sudden death were reported by Dolgin<sup>60</sup> and Holtz<sup>61</sup>. No cause of death was found in Cabot's<sup>62</sup> case.

#### OPHTHALMOLOGIC FINDINGS

In order to obtain some idea of the ocular changes in patients with this tumor, I examined all available case reports published in the last twenty years. There were many duplications. These were sometimes caused by an author's reporting the same case more than once, sometimes alone, sometimes with a collaborator. For example, a case reported by MacKeith<sup>4</sup> was reported again by Broster and MacKeith,<sup>63</sup> and at least 1 of Engel, Mencher and Engel's cases<sup>64</sup> was reported twice. Sometimes the same case appeared under a different authorship.

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57 Oberling, C, and Jung, G. Paraganglionoma Causing Fatal Obstetric Shock. Case, *Bull et mem Soc med d hop de Paris* **51** 366-371 (March 24) 1947.

58 Hick, F K. Suprarenalin-Producing Pheochromocytoma of Suprarenal Gland. Report of a Case, *Arch Path* **15** 665-674 (May) 1933.

59 Stevens, B F, and Waite, W W. Pheochromocytoma of Adrenal Gland. Case Report with Autopsy Findings, *Texas State J Med* **35** 469-471 (Nov) 1939.

60 Dolgin, W. Pheochromocytoma of Right Adrenal and Sudden Death Following Injury of Head. Case with Autopsy, *Arch Path* **40** 135-140 (Aug) 1945.

61 Holtz, E. Sudden Death of Patient with Pheochromocytoma of Adrenal Gland, *Deutsche Ztschr f d ges gerichtl Med* **32** 94-108, 1939.

62 Arteriosclerosis. Ganglion Neuroma of Adrenal, Cabot Case 17091, *New England J Med* **204** 447-453 (Feb 26) 1931.

63 Broster, L R, and MacKeith, R. Adrenosympathetic Syndrome (Pheochromocytoma with Paroxysmal Hypertension) with Transposition of Viscera, *Brit J Surg* **31** 393-395 (April) 1944.

64 Engel, F L, Mencher, W H, and Engel, C L. "Epinephrine Shock" as Manifestation of Pheochromocytoma of Adrenal Medulla. Report of Case with Successful Removal of Tumor, *Am J M Sc* **204** 649-661 (Nov) 1942.

Kalk's<sup>23</sup> case, for instance, was also reported by Buchner,<sup>65</sup> and Pincoffs' <sup>35</sup> case, by Shipley<sup>36</sup> Furthermore, it seemed advisable to omit the cases of malignant tumors with no hypertension, although those with hypertension were included Eventually, 108 suitable cases were collected When these were examined, it was found that in only 38 of them was there any mention of ocular signs or symptoms This, of course, does not indicate that in the remaining 70 cases an ophthalmologic examination was not made, it means merely that no mention of such an examination was included in the report For example, Cahill<sup>10</sup> noted in the body of his paper that vascular changes occur in the eyes He had found it necessary to omit such details from his protocols Sometimes an internist, in reporting the eyes as normal, was referring only to the external appearance In support of this, the paper of McCullagh and Engel<sup>53</sup> may be cited In the report of 1 case, they stated that the eyes were normal, but, in discussing the same case, they noted the presence of "eyeground changes of essential hypertension, grade I to II" Moreover, in the cases in which the fundi were called normal, it was not indicated whether or not the ophthalmoscopic examination was performed by an ophthalmologist Many internists use the ophthalmoscope well, but small irregularities in the lumens or other slight changes might easily elude them Sometimes examination was not feasible—all 3 of Kirschbaum and Balkin's<sup>32</sup> patients, for example, were comatose, and failure to perform ophthalmoscopic examinations is understandable However, Van Epps and his collaborators<sup>49</sup> gave no details of the visual acuity or findings in the fundus in a case in which vision was poor before operation and improved afterward

In all, the fundi were reported to have been normal in 12 cases—the cases of Padis<sup>6</sup> (2 of 3 cases), Stevens and Waite,<sup>59</sup> Bensis and Codonnis,<sup>66</sup> Strickler,<sup>42</sup> Hamilton,<sup>46</sup> Kelly and his co-workers,<sup>24</sup> Landau and his co-workers,<sup>50</sup> Kalk,<sup>23</sup> MacKenzie and McEachern<sup>51</sup> and Soffer and his collaborators (2 cases)<sup>67</sup>

In the 26 cases in which pathologic changes were found in the eyes, the descriptions were not always sufficiently detailed to serve as a guide to the pathologic process present Visual acuity was seldom recorded, and terminology was by no means standard It was not always clear whether spastic vessels were observed during or between attacks, and renal function at the time of examination was often not

65 Buchner, F Specific Tumors (Pheochromocytoma) of Adrenal Medulla with Hypertension Report of Two Cases, *Klin Wchnschr* **13** 617-619 (April 28) 1934

66 Bensis, W, and Codonnis, A Paroxysmal Hypertension Due to Medullo-suprarenoma Report of Case, *Bull Acad de méd, Paris* **121** 237-256 (Feb 21) 1939

67 Soffer, L, Mencher, W, and Colp, R Symposium on Surgical Diagnosis of Pheochromocytoma Two Cases with Operative Removal, *S Clin North America* **26** 368-381 (April) 1946



noted. The condition of the vessels immediately after operation was never mentioned, and the time of return of the fundi to normal was not stated. In only 1 case (Engel, Mencher and Engel<sup>64</sup>) was the posture noted at the time of examination. Nevertheless, a composite picture of the pathologic changes in the eye will be clear to the careful reader (table).

In all the cases in which the eyes showed abnormalities the arteries were found to be narrowed. In 9 of these cases only the vessels were affected. In 5 of the 9 cases the type of constriction was not noted (Allen,<sup>45</sup> Beer and his collaborators,<sup>68</sup> McCullagh and Engel<sup>53</sup> and Duncan<sup>27</sup> and Thorn,<sup>69</sup> and their associates), but in 2 of the 4 remain-

*Incidence of Pathologic Changes in the Eye in Cases of Pheochromocytoma  
of the Adrenal Gland Reported Since 1927*

		Number (per Cent) of Cases	
Cases of pheochromocytoma		103	
Cases in which ocular examination was noted		38	(35%)
Normal eyes		12	(32%)
Pathologic changes in eyes		26	(68%)
Vascular changes without retinopathy			
Narrowing (unspecified)	5		
Narrowing (spastic)	2		
Narrowing with blurring of disks	2		
	9	(35%)	
Vascular changes with retinopathy			
Hemorrhage only	3		
Exudate only	1		
Hemorrhage and exudate	1		
Retinal and optic nerve atrophy	1		
Papilledema, hemorrhage and exudate	9		
	15	(55%)	
Probable lesion of fundus	2	(7%)	

ing cases (Engel and his collaborators<sup>64</sup> and Wells and Boman<sup>10</sup>) spastic vessels and, in addition, blurring of the margins of the disks were present. Of the 15 cases in which retinopathy was found, retinitis of the so-called albuminuric type, with cotton wool patches, optic neuritis and hemorrhage, was present in 9 (Holst<sup>61</sup> [2 cases], Evans and Stewart,<sup>55</sup> Palmer and Castleman,<sup>70</sup> Brenner and his collaborators,<sup>71</sup>

68 Beer, E., King, F. H., and Prinzmetal, M. Pheochromocytoma of the Adrenal Gland with Demonstration of Pressor Substance (Adrenal or Epinephrin in Blood Preoperatively During Hypertensive Crises), *Ann Surg.* **106** 85-91 (July) 1937.

69 Thorn, G. W., Hindle, J. A., and Sandmeyer, J. A. Pheochromocytoma of Adrenal Gland Associated with Persistent Hypertension, *Ann Int Med* **21** 122-130 (July) 1944.

70 Palmer, R. S., and Castleman, B. Paraganglioma (Chromaffinoma, Pheochromocytoma) of Adrenal Gland Simulating Malignant Hypertension. Report of Case, *New England J Med* **219** 793-796 (Nov 17) 1938.

Hofmeyer,<sup>72</sup> Biskind and his collaborators,<sup>29</sup> Rodin<sup>73</sup> and deVries and his collaborators<sup>74</sup>) Hemorrhage alone was noted in 3 cases (Kvale and associates,<sup>38</sup> Collier and co-workers<sup>75</sup> and Binger and Craig<sup>54</sup>), exudate alone was noted by Evans<sup>76</sup>. Retinal and optic nerve atrophy was observed by Kremer<sup>77</sup>. Cases in which there was probably a pathologic condition of the fundus, but in which no examination was described, were reported by Mayo<sup>78</sup> and Van Epps and his co-workers.<sup>49</sup>

It is interesting to note that in Holst's<sup>61</sup> first case the severe changes were not present four weeks before the diagnosis was made. In Kremer's<sup>77</sup> case ocular changes were present two years before the diagnosis was established. In Evans' <sup>76</sup> case severe retinal lesions occurred in the absence of renal impairment, not an unusual finding. In Biskind's <sup>29</sup> case a "remarkable diminution in hemorrhage and exudate" occurred in the seven months following operation. In the case reported by de Vries and his co-workers,<sup>74</sup> there were found papilledema, arteriovenous compression, hemorrhages and exudate. Ten days after removal of the tumor the papilledema had become less pronounced. In two months the hemorrhages had absorbed, and in five months the papilledema had likewise disappeared. The white areas, which the authors stated to be degenerative, were still present seven months later.

For reasons already set forth, these figures show too many variables to permit their statistical use, but certain conclusions can be drawn. When the eyes of patients with pheochromocytoma of the adrenal gland were examined, 68 per cent showed pathologic changes, of eyes in which a pathologic process was found, 100 per cent showed vascular constrict-

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71 Brenner, F., Konzett, H., and Nagl, F. Pheochromocytoma of Adrenal Gland with Concomitant Neurofibromatosis. Report of Case, *Munchen med Wchnschr* **85** 914-916 (June 17) 1938.

72 Hoffmeyer, J. Two Forms of Adrenal Tumor and Their Possible Relation to Arteriosclerosis, *Virchows Arch f path Anat* **302** 627-639, 1938.

73 Rodin, F. H. Hypertensive Retinopathy Associated with Adrenal Medullary Tumor (Pheochromocytoma), *Arch Ophth* **34** 402-407 (Nov-Dec) 1945.

74 de Vries, A., Mandl, F., Rachmilevitz, M., and Ungar, H. Paroxysmal Hypertension Due to Medullary Tumor (Pheochromocytoma). Successful Operation, *Surgery* **19** 522-529 (April) 1946.

75 Collier, F. A., Field, H., Jr., and Durant, T. M. Chromaffin Cell Tumor of Adrenal Causing Paroxysmal Hypertension, Relieved by Operation, *Arch Surg* **28** 1136-1148 (June) 1934.

76 Evans, V. L. Suprarenal Tumor with Paroxysmal Hypertension. Case Report, *J Lab & Clin Med* **22** 1117-1120 (Aug) 1937.

77 Kremer, D. N. Medullary Tumor of Adrenal Glands, with Hypertension and Juvenile Arteriosclerosis, *Arch Int Med* **57** 999-1007 (May) 1936.

78 Mayo, C. H. Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve. Report of Case, *J A M A* **89** 1047-1050 (Sept 24) 1927.

tion, and 35 per cent showed lesions severe enough to be classified as albuminuric retinitis

The best description of these fundi in the literature is that of Rodin,<sup>78</sup> but his claim that they represent a "new clinical entity" is invalidated by the fact that they had been described in a score of papers before the publication of his report, in 1945

#### DIAGNOSIS

It has already been seen how the frequent coexistence of an increased basal metabolic rate and of hyperglycemia and glycosuria can prove misleading in arriving at a diagnosis of pheochromocytoma of the adrenal gland. How difficult this may be has been pointed out by Padis<sup>6</sup> and by Palmer and Castleman.<sup>70</sup> The commonest erroneous diagnosis seems to have been "essential hypertension" (hypertensive vascular disease), and because there were often pathologic findings in the urine during attacks it was believed that renal insufficiency had supervened. In the differential diagnosis, MacKeith<sup>4</sup> noted that in hypertensive vascular disease the paroxysms are gradual and the blood pressure remains high between attacks. Widespread symptoms are rare and are not easily precipitated by pressure, changes in posture or other excitants. It is imperative to keep in mind the urgency of early diagnosis. As Mencher (in his discussion on Hyman and Mencher<sup>48</sup>), Baumgarten and Cantor<sup>7</sup> and many others have pointed out, the hypertension becomes permanent after a while, and the blood pressure remains elevated between attacks. It has already been noted, and will be described later, how the effect of the disease on the retina offers an equally strong argument for early diagnosis.

Symptomatic paroxysmal hypertension may also occur with lead poisoning, eclampsia, tabes, angina pectoris, tumor of the thalamus, disorders of the vagus nerve and Nothnagel's syndrome.<sup>79</sup> The disease has also simulated gastric ulcer, shock, migraine and cerebral tumor (MacKeith<sup>4</sup>). Furthermore, the syndrome has frequently been associated with other diseases. Evangelesti's<sup>80</sup> patient had hemocytoblastoma (undifferentiated cell leukemia). Rosenthal and Willis<sup>81</sup> and others reported the coexistence of tuberculosis, and, of course, syphilis is

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79 This syndrome is characterized by coldness and numbness of the extremities, sweating, hypertension and bradycardia. It was first reported eighty years ago but was discussed and evaluated by Lewis (*Heart* 15 305-327 [July] 1931).

80 Evangelesti, T. Pheochromocytoma of Adrenal Gland in Case of Acute Hemocytoblastic Leukemia. Anatomicopathologic Study, *Arch "de Vecchi" per anat. pat. e med. clin.* 1 492-508, 1939.

81 Rosenthal, D. E., and Willis, R. A. Association of Chromaffin Tumors with Neurofibromatosis, *J. Path. & Bact.* 42 499-603 (May) 1936.

sometimes encountered (Labbé<sup>82</sup>) Diagnosis was made difficult in the case reported by Heath and his co-workers<sup>83</sup> by the concurrence of menopausal symptoms Barker's<sup>84</sup> patient had delusions and hallucinations, and these symptoms were also apparent in a patient under the observation of Perkins<sup>85</sup> In the case reported by Mortell and Whittle<sup>30</sup> convulsive seizures occurred

It is remarkable how often other tumors are found in conjunction with pheochromocytoma The commonest associated condition is neurofibromatosis This association was observed in cases reported by Rosenthal and Willis,<sup>81</sup> Kischbaum and Balkin,<sup>32</sup> Russum and Barry<sup>86</sup> and others In fact, Eisenberg and Wallenstein<sup>15</sup> collected 5 such cases (up to 1932), and in 1938 Bierner and his collaborators<sup>71</sup> found 8 cases of neurofibromatosis among 64 cases investigated Other tumors reported are cystadenoma of the pancreas, hypernephroma (carcinoma) of the kidney (which was contralateral to the pheochromocytoma), adenoma of the liver, colloid adenoma of the thyroid gland (Eisenberg and Wallenstein<sup>15</sup>) and sarcoma of the mediastinum (Russum and Barry<sup>86</sup>) In Lazarus and Eisenberg's<sup>9</sup> case carcinoma of the thyroid gland was present, and in the case reported by Lengeron and Delcour,<sup>17</sup> carcinoma of the esophagus Sometimes a mixed type of tumor seems to involve the adrenal cortex (either by extension or coincidentally), and associated symptoms suggestive of Cushing's syndrome (pituitary basophilism) have been reported by Hantschmann,<sup>87</sup> LeCompte<sup>88</sup> and others According to Cahill,<sup>10</sup> the positive diagnosis depends on (a) a typical paroxysmal attack, (b) clinical evidence that the attacks are produced by a pressor substance, (c) demonstration of the pressor substance in the blood and (d) roentgenologic evidence of the tumor on perirenal insufflation The last procedure has aroused a great deal of

82 Labbé, M Adrenal Tumors Causing Paroxysmal Arterial Hypertension, *Bull et mém Soc méd d hôp de Paris* **50** 1535-1537 (Dec 3) 1934

83 Heath, F K, Cahill, G F, and Atchley, D W Pheochromocytoma of the Adrenal Gland Correct Diagnosis and Successful Operation, *J A M A* **117** 1258-1260 (Oct 11) 1941

84 Barker, L F Cystic Tumor of Medulla of Suprarenal Gland (Paraganglioma), Associated with Early and Persistent Arterial Hypertension, With Arterial Thickening and With Multiple Hemorrhages Within Central Nervous System, Causing Epileptiform Convulsions, Paralysis, and Psychopathic State, *M Clin North America* **14** 265-268 (July) 1930

85 Perkins, O Personal communication to the author

86 Russum, B C, and Barry, M W Paraganglioma in Suprarenal Medulla with Neurofibromatosis, *Nebraska M J* **15** 243-244 (June) 1930

87 Hantschmann, L Tumors of the Adrenal Gland Associated with Hypertension, *Klin Wchnschr* **20** 394-398 (April 19) 1941

88 LeCompte, P M Cushing's Syndrome with Possible Pheochromocytoma Report of Case, *Am J Path* **20** 394-398 (April 19) 1941

discussion Cahill,<sup>10</sup> whose experience is wide, stated that he prefers it and it was recommended by Scholl and his co-workers<sup>5</sup> and many others. Mencher<sup>43</sup> has carried out the procedure more than one hundred times without mishap. Crane and his co-workers,<sup>48</sup> MacKeith<sup>4</sup> and others stated the belief that it was dangerous, and de Vries and his collaborators<sup>74</sup> recommended tomography. Fish (in his discussion on Roome<sup>89</sup>) suggested the substitution of oxygen for air. According to MacKeith,<sup>4</sup> the mass can be palpated in one third of the cases.

Chemical studies of the blood may be used in establishing the diagnosis. Following a suggestion credited by them to McQuarry, Wells and Boman<sup>19</sup> advocated estimating the serum potassium during an attack. This suggestion was based on the fact that intravenous injection of epinephrine may produce an increase in blood potassium of as much as 86 per cent. In MacKeith's<sup>4</sup> case the potassium measured 46 mg per hundred cubic centimeters. (The normal values are from 16 to 20 mg per hundred cubic centimeters.)

Treatment consists in surgical removal of the tumor. The operation is a serious one, but the deaths are increasingly less frequent of late. Here, again, statistics are hard to evaluate, as some of the patients died after operation and follow-up observations are not always given. At present, a rough estimate would put the chances of recovery at about 70 per cent.

Accounts of successful removal of the tumor may be found in the articles already cited, cases are also discussed in the papers of Volhard<sup>90</sup> and Suermondt.<sup>91</sup> Case reports analyzed but not specifically cited in the text, are to be found in the papers of Fingerland,<sup>92</sup> Hahn,<sup>93</sup> Römcke,<sup>94</sup> Nettleship,<sup>95</sup> Borrás and Meyer Mota<sup>96</sup> and Laubry and Bernal.<sup>97</sup> Excellent reviews have been presented by Bianchi<sup>98</sup> and

89 Roome N. Visualization of Adrenal Glands by Air Injection, *J A M A* **111** 1061-1065 (Sept 17) 1939

90 Volhard, F. Paroxysmal Hypertension Due to Medullary Tumor. Operation Followed by Recovery, *Munchen med Wchnschr* **91** 120 (March 10) 1944

91 Suermondt, W F. Paroxysmal Rise in Blood Pressure Cured by Removal of Tumor, *Zentralbl f Chir* **61** 70-74 (Jan 13) 1934

92 Fingerland, A. Pheochromocytoma of the Adrenal Gland. Report of Two Cases, *Virchows Arch f path Anat* **309** 218-234, 1942

93 Hahn, P. Pheochromocytoma of the Adrenal Gland. Report of Case, *Schweiz med Wchnschr* **72** 622-627 (June 6) 1942

94 Römcke, O. Paroxysmal Hypertension Due to Pheochromocytoma. Case, *Nord med (Norsk mag f lægevidensk)* **12** 2953-2956 (Oct 18) 1941

95 Nettleship, A. Medullary Tumor of the Adrenal Gland. Chromaffin Cell Tumor, *J Clin Endocrinol* **1** 124-125 (Feb) 1941

96 Borrás, P E, and Meyer Mota, M. Paraganglioma. Case, *Semana med* **1** 990-994 (May 5) 1938

97 Laubry, C, and Bernal, P. Paraganglioma of Adrenal Medulla. Case, *Bull et mem Soc med d hop de Paris* **50** 658-661 (May 21) 1934

Tanzella<sup>99</sup> Discussions are to be found in the reports of Biostei,<sup>100</sup> Gartner,<sup>101</sup> Bailaro,<sup>102</sup> Labbé and his co-workers,<sup>103</sup> Peyron<sup>104</sup> and Langeron and his collaborators<sup>105</sup> A symposium on the subject will be found under the names of Lian, Seguer and Girauld<sup>106</sup> and Welti<sup>107</sup>

#### REPORT OF CASES

CASE 1—J L, a girl aged 12, was admitted to the Babies Hospital on Sept 2, 1943, complaining of excessive perspiration and failure to gain weight for the last two years The family and past histories were noncontributory She had been well until two years prior to admission, when the parents noted that she perspired profusely The sweating was accompanied with polyphagia and polydipsia, but there was no polyuria The child became intolerant of heat and refused covers even on cold winter nights The parents maintained that she had not gained weight in the past two years and that during the few weeks before admission she had lost several pounds The patient had recently complained of her heart beating fast, but no dyspnea or other cardiac symptom was noted The child had not been as active as previously The parents noticed no tremor or exophthalmos The basal metabolic rates, determined on two occasions two weeks before her admission were reported to have been + 50 and + 30 per cent

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98 Bianchi, A E Paraganglioma of Adrenal Gland (Pheochromoblastoma), *An Inst modelo de clin med* **20** 361-392, 1939

99 Tanzella, A Adrenal Tumors and Hypertension Review of Literature, *Riv di clin med* **37** 663-669 (Oct 15-30) 1936

100 Broster, L R Tumors of Adrenal Gland, *Practitioner* **144** 135-142 (Feb) 1940

101 Gartner, W Clinical Picture, Especially Circulatory Disorders, in Paraganglioma, *Ztschr f Kreislaufforsch* **28** 82-90 (Feb 1) 1936

102 Barlaro, P M Relation of Cardiovascular Diseases and Endocrine Diseases Hypertension Associated with Adrenal Tumors, *Prensa med argent* **19** 331-337 (July 25) 1932

103 Labbé, M, Violle, P L, and Azerad, E Medullary Adenoma of Adrenal Gland with High Epinephrine Content and Paroxysmal High Blood Pressure (Gilbert Dreyfus), *Hôpital* **18** 472-474 (July) 1930 Labbé, M, and Nepveux, F Paroxysmal Hypertension of Adrenal Origin Case, *Bull et mem Soc med d hôp de Paris* **50** 337-347 (March 5) 1934

104 Peyron, A Paraganglioma and Its Cardiovascular Syndrome, *Bull Assoc franç p l'étude du cancer* **19** 618-650 (July) 1930

105 Langeron, L, Paget, M, and Lohéac, P Estimation of Epinephrine in Tumors Relation to Histologic Structure of Tumor and Blood Pressure of Subject, Three Cases, *Compt rend Soc de biol* **100** 873-875 (April 8) 1929

106 Lian, C, Seguer, F, and Girauld, A Diagnostic Possibilities of Questioning Patient with Common Forms of Paroxysmal Arterial Hypertension Due to Paraganglioma, *Semaine d hôp, Paris* **22** 7 (Jan 7) 1946, Paradoxical Circulatory Collapse and Sudden Death in Course of Paroxysmal Arterial Hypertension Due to Paraganglioma, *ibid* **22** 7-10 (Jan 7) 1946, Paroxysmal Arterial Hypertension Due to Paraganglioma General Survey, *ibid* **22** 1-3 (Jan 7) 1946

107 Lian, C, Welti, H, and Seguer, F Paroxysmal Arterial Hypertension Due to Paraganglioma Case, *Semaine d hôp, Paris* **22** 3-6 (Jan 7) 1946 Welti, H Surgical Treatment of Paroxysmal Arterial Hypertension Due to Paraganglioma *ibid* **22** 13-15 (Jan 7) 1946

The patient was well developed but thin, the skin was warm and moist, with little subcutaneous fat. The temperature was 100 F, the pulse rate 108, the respiratory rate 24 and the blood pressure 180 systolic and 120 diastolic in the left arm and 210 systolic and 150 diastolic in the left leg. The thyroid was not enlarged but was palpable. There were no nodules or swelling. The heart was not enlarged, the rate was rapid, the sounds were of good quality, and there were no murmurs. The liver was palpable 2 cm below the costal margin. The remainder of the physical examination revealed nothing abnormal.

Results of laboratory tests were as follows: hemoglobin, 96 per cent, white blood cells, 8,850, polymorphonuclear leukocytes, 62 per cent, lymphocytes, 38 per cent. The urine showed a faint trace of albumin and an occasional white blood cell. The tuberculin test gave a negative reaction. The fasting blood sugar was 88 mg and the nonprotein nitrogen 34.6 mg, per hundred cubic centimeters. Creatine-creatinine studies showed a ratio of creatine to total creatinine of about 0.4. The serum iodine was 4.8 micrograms per hundred cubic centimeters (normal value for girls of this age, 6.2 micrograms per hundred cubic centimeters). The basal metabolic rates were +51.1 and +56.8 per cent on successive days. The blood pressure was taken by a number of observers and was always in the range of the original reading. The blood pressure when the patient was sitting or standing was much lower than when she was lying down. It was raised by immersion of the limbs in ice water, was lowered by pressure on the abdomen and was unaffected by pressure on the carotid artery. Injection of 0.2 cc of epinephrine hydrochloride (1:1,000) intravenously produced immediate subjective complaints of headache and nausea, the blood pressure rose sharply after administration but returned to initial levels in twenty minutes. The patient was discharged without final diagnosis, and on two subsequent admissions little change in her condition was found except that on one occasion the blood pressure was found to be 240 systolic and 150 diastolic and the basal metabolic rate +67 per cent.

The patient was readmitted on Aug. 3, 1944. In the interval her condition had remained unchanged. Results of an intravenous pyelographic examination showed that the pelves and calyces were normal except for slight ectasis of the left pelvis. A flat roentgenogram of the abdomen showed that the renal and adrenal shadows were not clearly outlined. In the region of the shadow of the left adrenal gland there was a single, small shadow of the density of calcium. On August 14 both flanks were injected with air. The kidneys were found to be well outlined, but there was considerable enlargement in the region of the left adrenal gland in both the immediate and the twenty-four hour roentgenogram. On August 17 an exploration of the left adrenal gland was made by Dr. George F. Cahill, with excision of the tumor of the left adrenal gland. After the operation the temperature rose to 104.6 F but quickly fell to normal. The wound healed satisfactorily, and on the twenty-third postoperative day the patient was discharged. There was no significant drop in her blood pressure, which was 172 systolic and 144 diastolic at the time of her discharge, on Sept. 9, 1944.

The pathologist, Dr. A. P. Stout, reported that the tumor was a pheochromocytoma.

The patient was readmitted on Oct. 4, 1944 because her blood pressure had not fallen below 174 systolic and 140 diastolic and it was felt that residual epinephrine-producing neoplastic tissue had been left behind. On October 10 the patient was given intravenous injections of the benzodioxane drugs 1164 F (dimethyl-2,4-piperidinomethylbenzodioxane) and 933 F (piperidylmethyl benzodioxane). The former, which has an adrenolytic and a sympatholytic action, was used because it

had been controlled by experiments on patients with hypertensive vascular tissue, in whom it uniformly failed to lower the blood pressure. The blood pressure was lowered in the present case. It was considered that the hypertension exhibited by the patient was caused by excessive amounts of circulating epinephrine. On October 13 an attempt was made to assay the patient's blood for epinephrine by measuring its effect on the blood pressure of a cat. The experiment failed to reveal the presence of epinephrine in her blood but indicated that the blood contained a factor which had a lethal effect on the cat.

On October 19 an exploration of the retroperitoneal space was carried out by Dr Cahill. A tumor was encountered cephalad and mesial to the left adrenal gland in the retroperitoneal space and was removed. After operation, the blood pressure fell to a level of 138 systolic and 100 diastolic. The patient was symptomatically much improved. There was cessation of excessive diaphoresis and absence of headache and palpitation. She was discharged on the sixteenth postoperative day.

The pathologic report of the excised tumor, by Dr M. M. Melicow, stated that the characteristics were essentially those of the original tumor.

Since the second operation the patient has done well. When last seen, on April 7, 1946, her blood pressure was 116 systolic and 78 diastolic, her pulse rate 92 and her weight 92½ pounds (42 Kg), and she was entirely devoid of symptoms.

*Ophthalmic Study*—The eyes were examined on July 1, 1944, by Dr James McGraw. The margins of the disks were blurred, and there was at least 1 D of elevation. The arteries were conspicuously narrowed, and areas of scattered spasm were seen. There was slight arteriovenous notching. Nasal to the right disk were several fluffy white exudates, and to the left lay a small, flame-shaped hemorrhage. The peripheral fields were normal and the blindspots perhaps a little enlarged. Vision was 20/20 in each eye. On September 9 the same observer noted that there had been considerable visual loss, the vision now being reduced to 20/70 in the right eye and 20/40 in the left eye. The fundi were approximately the same as before. On October 11 star-shaped exudates were observed between the disk and the macula. The hemorrhages had been absorbed, but the arteries had become more tortuous. In the meantime, however, the papilledema had increased to 3 D. Vision was 20/40 in the right eye and 20/50 in the left eye. Dr McGraw's impression on this occasion was that the process had reached the stage of hypertensive retinopathy grade III. On October 24, Dr McGraw noted that there was no perceptible change in the appearance of the fundi.

On November 22, a month after the second operation, the vision had increased to 20/30 in the right eye and 20/20 in the left eye. The papilledema had nearly subsided. Notes as to the spasticity of the arteries, unfortunately, were not made on this occasion. On Oct 8, 1945, vision was 20/20 in each eye. The retinopathy had almost entirely cleared, and the spasm of the blood vessels had completely disappeared. An occasional exudate was seen around the maculas. When she was last seen, on April 2, 1946, the vision and fundi were entirely normal.

CASE 2—D. B., a 10 year old Negro girl, was admitted to Babies Hospital on Feb 20, 1946. For three years the child had had nervous attacks and episodes of perspiration. The present illness was first noticed when, on walking up a hill to school, the child would become extremely nervous, exhausted and breathless and would complain of a pain in the epigastrium. She would vomit and the mother would put her to bed, at which time the child was sweating profusely. After she had calmed down, she was apparently as well as before. The mother expressed



the belief that the attacks were correlated with emotional factors rather than with physical exertion, for example, the child could climb the stairs at home without being exhausted. The attacks occurred every week, and for two years the mother took the child to a clinic. There no definite diagnosis was made, but the child was carried as an outpatient without treatment except for advice about resting and diet. The physician there found the blood pressure to be low. The child continued to have attacks at home, and sometimes at school, until she was seen by a cardiologist, who found an enlarged heart on fluoroscopic examination and advised admission to another hospital. She was hospitalized elsewhere three or four months later and remained there until admitted to the Babies Hospital. The symptoms had not changed during this period. While in the other hospital, she underwent a benzo-dioxane test. The blood pressure, both systolic and diastolic, fell 50 mm and remained depressed for ten minutes.

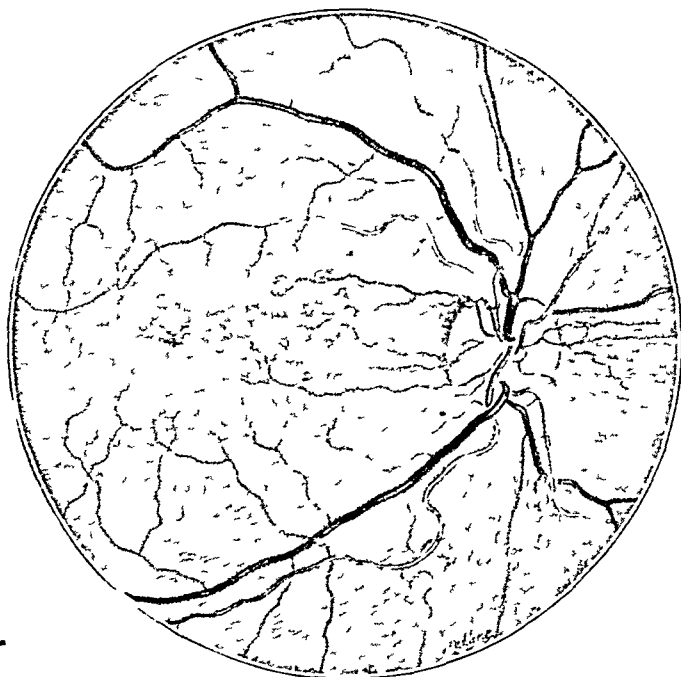


Fig 1—Fundus in case 2

Physical examination showed that the child was well developed and well nourished and in no apparent discomfort. The skin was dry and slightly scaly over the back and front of the chest. Her throat was clear, and the tonsils were small. Several small submaxillary lymph nodes were found. The chest was symmetric, and there was no precordial bulge. The heart was slightly overactive, the impulse was moderately forceful, and there were no thrills. Sounds over the base were of good quality. The second pulmonic sound was slightly louder than the second aortic sound. Over the lower part of the precordium every other first sound was heard as a bit softer. The pulse rate was 96 per minute. Over the apical region there was a soft, slow, blowing systolic murmur, localized to a small area. There were occasional extrasystoles. Pulsation of the femoral artery was easily felt. The blood pressure was 182 systolic and 130 diastolic in the right arm and 180 systolic and 130 diastolic in the left arm. The abdomen was soft and was slightly tender in the upper left and middle quadrants on deep palpation. There was no

apparent tenderness in the costovertebral angle. The edge of the liver was palpable, but no tumor was felt. The blood pressure readings taken with massage of the abdomen were as follows: Left side—base line reading, 186 systolic and 146 diastolic, readings at one minute intervals, 192, 202, 210, 198, 194 and 182 systolic and 148, 150, 160, 148, 146, and 136 diastolic. Right side—base line reading, 176 systolic and 122 diastolic, at ten seconds, 178 systolic and 130 diastolic, at one minute, 182 systolic and 134 diastolic, at two minutes, 182 systolic and 132 diastolic, at three minutes, 180 systolic and 130 diastolic. Special examinations of the heart, including electrocardiographic and roentgenographic studies, revealed the following signs: a prominent bulge in the cardiac shadow in the left ventricle without evidence of enlargement of the left auricle, pulsus alternans, occasional extrasystole and sinus tachycardia.

An aerogram of the adrenal glands showed no definite enlargement. A roentgenogram of the upper part of the genitourinary tract showed the lumbar portion of the spine to be normal. The outlines of the psoas muscle were distinct. Both kidneys could be partially visualized. The right appeared normal in size, shape and position, the left was somewhat enlarged and appeared to be lower than normal. A roentgenogram of the lower part of the genitourinary tract revealed nothing abnormal. An intravenous pyelogram showed good function bilaterally. Laboratory tests revealed the following values: hemoglobin, 12.2 Gm per hundred cubic centimeters, or 84 per cent, red blood cells, 4,390,000, and white blood cells, 13,400, with 73 polymorphonuclear leukocytes. The urine was normal. The nonprotein nitrogen was 30.6 mg per hundred cubic centimeters. The serum sodium measured 131 mg and the serum potassium 4.5 mg, per hundred cubic centimeters. The sedimentation rate was 13 mm in one hour. The reaction to the Kline test was negative.

The patient was in the hospital for thirty days, during which time the blood pressure showed a wide fluctuation, the systolic ranging from 150 to 250 and the diastolic from 90 to 150 mm. Such variations were independent of external stimuli. Episodes of diaphoresis and nervousness continued. The pulse rate fluctuated from 100 to 120 per minute. The temperature was constantly normal. Pulsus alternans continued, and the cardiac reserve appeared to be gradually diminishing. On the thirtieth day after the patient's admission, using tribromoethanol solution U.S.P. induction and ether anesthesia, Dr. Cahill made an exploration of the adrenal glands. No tumor was observed in the right adrenal. A small, palpable, rounded mass was observed retroperitoneally on the right side, apparently at the bifurcation of the aorta. A mass, the size of a large orange, was noted in the right epigastric area. This was deep red and was covered with cirroid, dilated veins. The slightest touch of this mass was accompanied with a notable increase in the rate and volume of aortic pulsation. The mass was seen to extend backward along the vertebra, deep into the right lateral vertebral space. It was independent of the kidney and the adrenal gland. Every attempt to handle the mass was accompanied with alterations in the pulse, as determined in the abdominal aorta. The anterior veins were ligated doubly and incised, at this period the patient's pulse ceased. Attempts were made to stimulate the heart, which apparently was in contraction. Artificial respiration was given, but the patient died.

The pathologist, Dr. C. H. Lynch, reported a pheochromocytoma. Autopsy, performed by Dr. Beryl H. Paige, revealed that between the adrenal glands and the upper poles of the kidneys was a tumor 5 cm in its greatest diameter. The anterior surface of this mass was soft and friable and blood stained in places, and pale yellow in others. The myocardium of the left ventricle was greatly hypertrophied, but the cusps of the aortic valve were normal. No definite nephritis was demonstrated.

*Ophthalmic Examination*—Prior to the patient's admission, the following note had been made "Examination of the fundi revealed arteriolar spasm with 'silver wire' veins, there was no papilledema, hemorrhage or exudate" On Feb 26, 1944, she was examined by Dr J P Macine He found the disks somewhat hyperemic but fairly distinct Physiologic excavations were present There was generalized narrowing of the arterioles, with banding, tortuosity and increased reflexes Notching of the veins<sup>6</sup> was present There was beginning formation of a star between the disk and the macula in the right eye No hemorrhages were seen

CASE 3—P D, a boy aged 12 years, was admitted to the Babies Hospital on Oct 4, 1946, with the complaint of failure of vision for one week The family history was irrelevant The patient had had two convulsions in infancy, one at 12 months and the other at 15 months of age, each occurring during a febrile infection of the upper respiratory tract He had had chickenpox and measles A gangrenous appendix was removed in 1942, and the same year he had been struck on the top of the head by a thrown brick, receiving a severe laceration of the scalp The following year he had been thrown from a horse, and in 1945 he had been hit above the left eye by a golf ball, with resulting laceration

One week before admission the patient began to complain of poor vision, saying that the objects in the room were blurred and that he could not read large print in books He was examined on the day of admission by his ophthalmologist, Dr R N Berke, who found papilledema, hemorrhages and exudate in both eyes The patient had been noted to have excessive diaphoresis and thirst during the previous three years, symptoms associated with emotional crises resulting from such events as acting as altar boy in church Symptoms had become severer during the past summer About two years before he began to have episodes ushered in by severe, pounding headache, which was quickly associated with generalized constant aching abdominal pain, nausea, vomiting, sometimes pallor and "pounding heart" These symptoms occurred about once a month, lasted a day or so and were followed by another day or two of weakness, diaphoresis and loss of appetite Attacks were precipitated, it seemed, by excitement or anticipation of an event such as a boy scout hike, school play or confirmation, and almost invariably he became so ill that he was unable to participate in the event No attacks occurred from June 1946 until the present episode A blood pressure reading taken by a nurse in June, during an interval of freedom from the symptoms, was reported as "normal"

During the month before his admission the patient seemed to tire easily and was weak on arising in the morning On admission, he appeared to be well nourished and well developed, he was ambulatory, did not seem acutely ill, was mentally alert, cooperative and pleasant and was apparently of normal intelligence The temperature was 99 F, the pulse rate 80, the respiratory rate 24 and the blood pressure 260 systolic and 190 diastolic in both the arms and the legs Examination of the heart showed that the point of maximum impulse was in the fifth interspace, about 1 cm to the left of the nipple line It was forceful and easily visible No enlargement of the heart was apparent on percussion The aortic second sound was very loud, louder than the second pulmonic sound No murmurs were heard The lungs appeared clear on percussion and auscultation The abdomen was soft, and the liver, kidney and spleen were not felt No masses were palpated except for feces in the left lower quadrant There was a well healed scar at McBurney's point, and no tenderness was elicited The genitalia were normal and prepubescent

The laboratory findings were as follows hemoglobin, 15 Gm per hundred cubic centimeters, red blood cells, 5,500,000, white blood cells, 17,800, polymorpho-

nuclear cells, 41 per cent, lymphocytes, 52 per cent, monocytes, 5 per cent, eosinophils, 1 per cent, basophils, 1 per cent. The Schilling count was as follows: no myelocytes, 9 stab forms and 33 mature neutrophils, there was no stippling. Examination of the urine showed a  $p_H$  of 6, a specific gravity of 1.010 and absence of albumin, sugar and acetone, amorphous material was revealed on microscopic examination. Subsequent urinalysis revealed an occasional mixed cast. Chemical analysis of the blood showed nonprotein nitrogen, 37.2 mg, sugar, 99 mg, serum albumin, 5.34 Gm, and globulin 2.72 Gm, per hundred cubic centimeters. The sedimentation rate was 14 mm in one hour. The reaction to the subcutaneous injection of 0.01 mg of old tuberculin was negative.

On Oct 14, 1946, a roentgenogram of the skull revealed no visible abnormalities. A roentgenogram of the knees on October 5 revealed no abnormalities and no

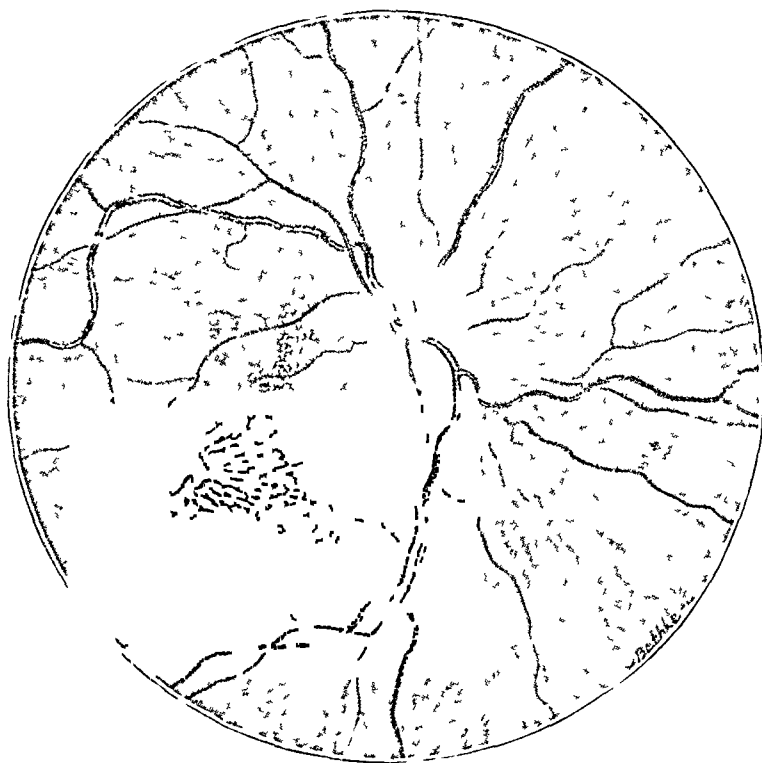


Fig 2—Fundus in case 3

evidence of renal osteodystrophy or generalized rarefaction. There was a cortical defect on the medial aspect of the shaft of the femur. No roentgenologic evidence of calcification was seen in the region of the adrenal glands. The heart shadow was small. An aerogram on October 10 showed diffusion of air about both kidneys, but no enlargement of the adrenal gland was demonstrated on either side. The right kidney was somewhat small. An aerogram of the right side on October 12, forty-eight hours later, showed that the renal area was still not distinct, but there was possibly slight enlargement of the adrenal gland. Two shotlike areas of increased density were lying to the left of the spine. An intravenous pyelogram (October 16) showed a hypoplastic right kidney.

An electroencephalogram (October 7) showed "bursts of high voltage, 3 per second activity appearing synchronously in all leads, and transient focal signs in the right parietal area." An electrocardiogram (October 14) showed "left axis deviation and prolonged conduction."

The patient's physical findings and complaints did not change until the third day in the hospital, when he began to have episodes of generalized abdominal pain, associated with severe pounding headache, pallor, sweating, nausea, vomiting and retching. During the most violent of these attacks his pulse was 140 and his blood pressure 270 systolic and 210 diastolic. The abdomen was not palpated during these episodes because of the possibility of pheochromocytoma. Intravenous injection of magnesium sulfate did not seem to affect the blood-pressure. On the fifth day in the hospital the blood pressure had dropped to 168 systolic and 134 diastolic. His acute symptoms had subsided, and he was pale, listless and unwilling to eat. A recording of his blood pressure after the injection of 12 mg of a benzodioxane derivative showed a drop to 138 systolic and 110 diastolic fifty-five seconds after injection, with almost immediate return to the original level of 162 systolic and 128 diastolic. On the eighth day in the hospital the blood pressure had dropped to 118 systolic and 82 diastolic, and the first aerogram was taken by Dr Cahill, showing the left kidney to be well delineated but the right kidney to be surrounded with air only over the lower pole. On the ninth day in the hospital the patient was noted to be reading the "funny books." He was alert and free from all complaints.

On the sixteenth day in the hospital cystoscopic examination, made with the patient under anesthesia, revealed that the bladder and ureters were normal. A pyelogram indicated hypoplasia of the right kidney. A second aerogram of the right side showed that the renal area was still not distinctly seen. On the twenty-third day in the hospital the patient was up and moved about with ease, without complaint. The blood pressure ranged from 120 systolic and 100 diastolic to 170 systolic and 100 diastolic. On the twenty-sixth day in the hospital he was taken to the operating room, with tribromoethanol solution-nitrous oxide and oxygen induction, with supplementary anesthesia induced with intravenous injection of "pentothal sodium," the abdominal cavity was opened by Dr George F Cahill. It was observed that the left kidney was enlarged and that the left adrenal gland was not remarkable, the right kidney was hypoplastic and exhibited a mass about 5 by 5 cm, with a fibrous capsule attached to the renal pedicle and overlying the vena cava. The right adrenal gland was not remarkable. The right kidney and the attached mass were excised. During the entire procedure the blood pressure remained relatively stable and exhibited no untoward rise or decline. A continuous intravenous drip of isotonic sodium chloride solution USP was maintained during the latter half of the operation, and 500 cc of whole blood was given by transfusion. The immediate postoperative condition was good.

Immediately after the operation, and for the succeeding three days, the temperature was 101 to 103 F and then suddenly fell to normal and remained so. The patient was given a course of injections of penicillin, 20,000 units intramuscularly every three hours during this period. Except for this febrile episode, the postoperative course was uneventful. The blood pressure remained about 120 systolic and 80 diastolic. On the ninth postoperative day, another trial of a benzodioxane derivative was given intravenously, with the blood pressure ranging from 118 to 124 systolic and 90 to 100 diastolic. There was no significant fall or rise after the drug (0.6 cc) had been given. The surgical wound healed well, and the urine was normal. The patient was up and about for a week prior to his discharge, during which time he was without complaint, ate well and gained weight. He was discharged, in good condition, on the fourteenth postoperative day, or the fortieth day in the hospital.

The pathologist, Dr M M Melicow, made the report of pheochromocytoma of aberrant adrenal medullary tissue

*Ophthalmic Examination*—I examined the patient's eyes on Oct 5, 1946, when they appeared externally normal. In the right eye, the nerve head was somewhat pale and striated, and the papilledema measured 3 to 4 D. There was an area of exudate between the edematous disk and the macula, arranged roughly in the form of an inverted fan, so that the apex was centered on the macula. This exudate was rather fluffy in appearance, but the macula itself was occupied by a dense white plaque, which was slightly refractile. A small hemorrhage was seen just nasal to the disk. At the periphery two minute areas of old choroiditis were observed. The arterioles were greatly narrowed, and the arteriovenous ratio was about 1:2. This narrowing was largely uniform, although in places, notably along the course of the inferotemporal artery at the edge of the edematous disk, there was almost complete occlusion. The light reflex was not notably increased, but there was distinct denting of the veins with no definite sclerotic phenomena at the crossings.

In the left eye the findings were essentially the same except that the macula seemed to have escaped and no chorioretinal lesions were observed. The child was in bed and ill, and no attempt was made to determine the visual fields or to measure the visual acuity.

I saw the patient again on October 9 on which occasion he was much better and his blood pressure had temporarily fallen to 140 systolic. At this examination I got the impression that the arteries were somewhat larger, and the arteriovenous ratio was approximately 2:3. On October 14 the blood pressure was 120 systolic. On this occasion I noted that the hemorrhage had been absorbed and the vessels were definitely larger. The exudate was of about the same extent but less fluffy in appearance, and was, indeed, beginning to resemble that seen in diabetic retinopathy. The papilledema was unchanged. The vessels were definitely larger, and there was no evidence of spasticity. Vision was 20/200 in the right eye and 20/50 in the left eye, unimproved by correction. The visual field in the left eye showed a normal periphery, but the right eye showed considerable defect in the inferonasal sector.

The patient was next seen on Nov 4, 1945, at which time the hemorrhage was absorbed, the papilledema was subsiding and the exudate, while perhaps somewhat diminished, showed no decided change. He was last seen on Jan 24, 1947. His blood pressure was 116 systolic and 80 diastolic. Vision was 20/50 in the right eye and 20/25 in the left eye, unimproved. Examination of the interior showed that the papilledema had subsided. The exudate in the right eye was greatly reduced, although there were remnants of the star figure and the macula was still involved. The disks were of fair color, although slightly pale. In the left eye there was scattered exudate, which was rather white and powdery between the disk and the macula. The arteries were entirely normal. There was no denting of the veins. The field in the right eye was normal at the periphery, and the blindspot was not enlarged. A small, wedge-shaped defect remained, however, in the inferonasal quadrant of the right visual field.

#### SUMMARY AND CONCLUSIONS

The literature on pheochromocytoma of the adrenal gland is reviewed with special reference to pathologic changes in the eye. The dominant finding in cases of this tumor is vascular hypertension in the course of

which pathologic changes may be found in the retina or in its blood vessels or in both. The findings cannot be differentiated ophthalmologically from those encountered with hypertensive vascular disease ("essential hypertension"). Because the ocular symptoms may be the first, or indeed the only, sign of the disease, the ophthalmologist will often be seen before the internist, and, regardless of the time of its appearance, the onset of failing vision will sooner or later bring him into consultation. The possibility of pheochromocytoma should be considered whenever he finds evidence of vascular disease.

Three cases in children, all with pathologic changes in the retina, are reported.

Dr George F Cahill, Dr Howard H Mason and Dr Raynold C Berke permitted me to report these cases.

# PROPTOSIS DUE TO NEUROBLASTOMA OF THE ADRENAL CORTEX (HUTCHINSON'S SYNDROME)

Report of a Case

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**N**EUROBLASTOMA of the adrenal gland with its subsequent metastases is a serious disease which occurs almost entirely in children. It is of great interest to ophthalmologists because of its metastasis to the orbit, with resultant proptosis, discoloration of the lids and loss of vision, its rarity, its rapidly fatal termination, and its insidiousness and concealment of the primary lesion, causing difficulty in diagnosis in the early stages. The orbit is invariably involved in the metastases, and frequently it is the eye which gives the first noticeable indication of the disease.

Less than 4 cases a year have been recorded since Vinchow<sup>1</sup> discovered his case in 1864, the total number reported up to the end of 1940 being only 291.

The clinical course in cases of this disease is almost universally rapid, progressing to fatal termination. The average duration of the symptoms and signs is two to five months. The average age of patients with the Pepper type, which metastasizes to the mesenteric nodes and the liver, is 6 months, and that for the Hutchinson type, three years and 10 months. It is noteworthy that with the Pepper type the duration is shorter and the age of the patient less than with the Hutchinson type.

The concealment of the primary tumor until its discovery at autopsy is an important feature. The orbital edema and the proptosis are usually the only symptoms noticed at first. As a rule, no abdominal tumor can be palpated early in the disease, of 10 cases described in Hutchinson's original article,<sup>2</sup> an abdominal tumor was palpated in only 5. In most of the cases the first diagnosis is made late in the illness, when metastases are pronounced.

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<sup>1</sup> Virchow, R. L. Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-1867, vol. 2, p. 150.

<sup>2</sup> Hutchinson, R. Suprarenal Sarcoma in Children with Metastases in the Skull, Quart. J. Med. 1 33, 1907.



## REPORT OF CASE

*History*—H C, a white boy 15 months of age, was admitted to the hospital on Aug 22, 1944. According to the mother, the child was apparently normal until July 1944, when he had fever which was ascribed to a streptococcic infection of the throat and which lasted one week. At this time the mother noticed that the left eye was more prominent than the right.

The family and past histories were essentially noncontributory.

*Examination*—Physical examination revealed a mass in the upper left quadrant of the abdomen, enlarged glands at each angle of the jaw, an enlarged, rubbery parotid gland on the right side, and pronounced proptosis of the left eye.

The blood count showed a hemoglobin concentration of 56 per cent but otherwise nothing abnormal. The urine was essentially normal.



Fig 1—Characteristic proptosis and edema in a case of Hutchinson's syndrome

*Roentgenologic Report*—Skull and Face. There was a good deal of swelling of soft tissues in the region of the left orbit. Destruction of portions of the facial bones had occurred on the left side, extending posteriorly to involve the ethmoid and sphenoid bones and portions of the frontal bone. These destructive processes were the result of a tumor growing in this region, which was thought to be a neuroblastoma.

*Long Bones*. Radiolucent areas were present in the upper ends of the humerus and femur on each side, indicating that the destructive processes in the bone were metastatic.

*Diagnosis*—The provisional anatomic diagnosis was neuroblastoma of the left adrenal gland, with invasion of the left renal pelvis, metastases to the retroperitoneal lymph nodes, the liver, the cervical lymph nodes, the right side of the mandible and the left orbit (with extensive destruction), causing extreme proptosis, and compression of the right frontal lobe by a large metastatic lesion in the skull.

*Course of Illness*—On the patient's admission to the hospital, it was the consensus that the disease was Hutchinson's syndrome. On consultation, I was advised that treatment would be of no avail. The course of the patient's condition was progressively downhill, the proptosis increased, and the patient gradually became more lethargic. Death occurred forty days after his admission.

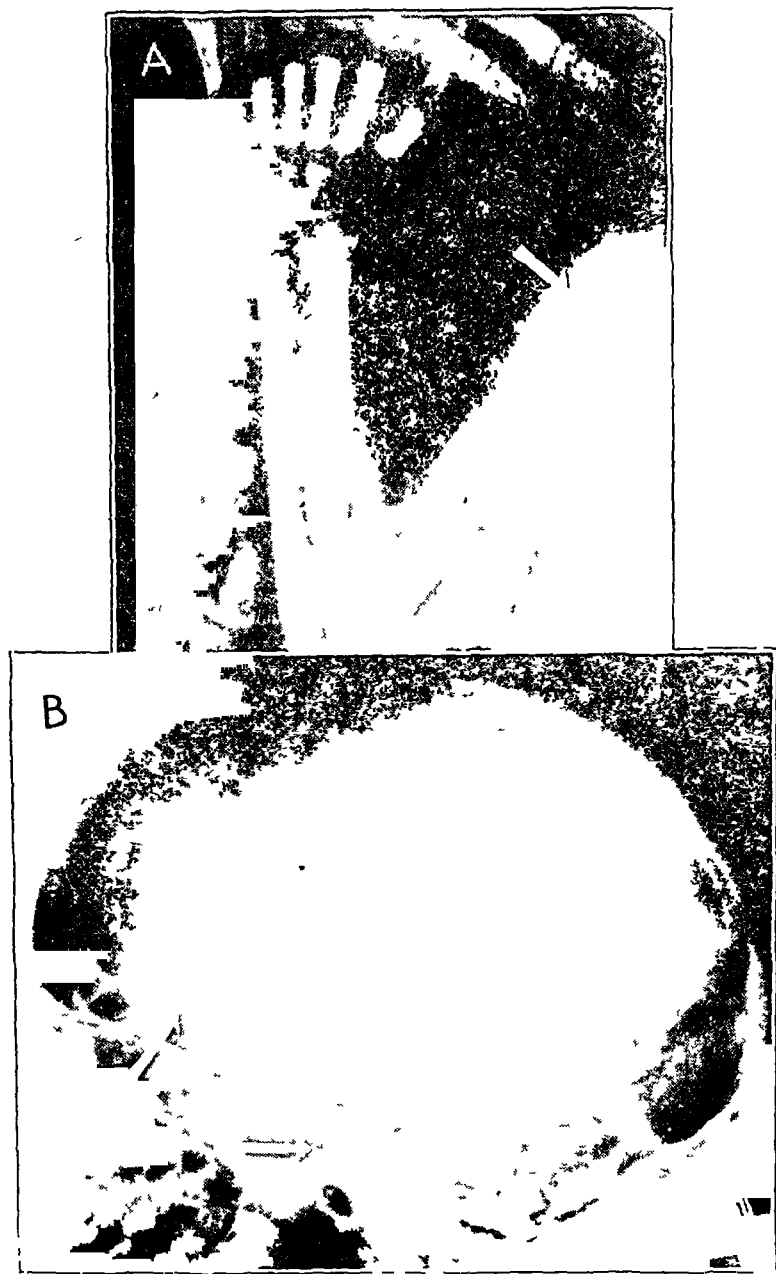


Fig 2—*A*, radiolucent areas in the humerus, *B*, destructive processes in the skull, resulting from metastases from the neuroblastoma (arrows)

*Report of Autopsy*—Autopsy revealed neuroblastoma of the left adrenal gland, with invasion of the left renal pelvis, metastases to the retroperitoneal lymph nodes, the right side of the mandible and the left orbit (with extensive destruction), causing extreme proptosis of the eye, and compression of the right frontal lobe by a large metastatic lesion of the skull.

## COMMENT

Malignant tumors in the region of the adrenal glands are not uncommon in children. The majority of such tumors are composed of embryonically young cells, derived from the sympathetic nervous system, which metastasize so readily that the outcome is almost invariably fatal. To these neoplasms the terms neurocytoma, neuroblastoma, sympathogonioma and sympathicoblastoma have been applied. Less common is the ganglioneuroma, a tumor of similar origin but not highly differentiated.

Virchow<sup>1</sup> is credited with being the first to recognize the nature of these tumors of the adrenal cortex in children. Prior to his work the neoplasm was not considered to be of nervous origin but was thought to be a round cell sarcoma of the adrenal gland. Virchow referred to the tumor as a glioma. To Hutchinson,<sup>2</sup> in 1907, and Pepper,<sup>3</sup> in 1910, goes the credit of effectively describing the clinical picture of this disease. Wright and Page<sup>4</sup> were the first to use the term neuroblastoma. In 1910 they established the theory of the neuroblastic origin of this tumor. Kato and Wachter<sup>5</sup> recently reviewed a fairly large number of the reported cases in order to determine whether the tumor was a neuroblastoma. In some cases the clinical diagnosis seemed correct but the histologic features were incompatible with those of a true neuroblastoma.

The various types of tumors arising from the adrenal gland may be traceable to the development of that gland. The adrenal cortex is derived from the mesoderm of the wolffian ridge, but the adrenal medulla has an entirely different origin—the ectoderm of the primitive neural crest. The neural crest gives rise to two types of cells—the stationary cells, which develop into the cells of the dorsal root ganglions, and the migrating cells, from which the sympathetic ganglion cytons and the chromaffin cells of the adrenal medulla are derived. The undifferentiated migratory cells are sympathetic neuroblasts. Tumors composed of undifferentiated neural cells are usually neuroblastomas and are highly malignant. Tumors made up of differentiated cells are benign and may be composed of mature nerve cells and fibers (ganglioneuroma), of chromaffin cells (paraganglioma) or of elements of chromaffin cell structure (pheochromocytoma).

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3 Pepper, W. A. Study of Congenital Sarcoma of the Liver and Suprarenal, *Am J M Sc* **121** 287, 1901.

4 Wright, F. H., and Page, B. H. Neurogenic Tumors of the Sympathetic Nervous System in Children. A Report of Three Cases Surviving a Year or Longer, *J Pediat* **14** 137, 1939.

5 Kato, K., and Wachter, H. E. Adrenal Sympathetic Blastoma in Children, *J Pediat* **12** 449, 1938.

Metastases are widespread. In the Pepper type the mesenteric lymph nodes and the liver are predominantly involved, in the Hutchinson type the skull and the periorbital area are particularly affected. Originally, the tumor may resemble the ganglioneuroma, and the metastases have a typical neuroblastomatous formation.

Clinically, anemia is a striking factor in all cases, the changes in the blood being thought of representing as a profound secondary anemia. Leukocytosis was not recorded in any case. An abdominal tumor in either loin was found in only half the cases. In two thirds of the cases proptosis or discoloration of the eyelids on one or both sides was reported. The progress of the disease was rapid in every instance, the younger the child, the more rapid the course appeared to have been. The duration of life from the time the earliest signs were observed was about six months for the oldest child and only one month for the youngest. The advance of the growth is characterized by progressive exhaustion and anemia and by indications of increased intracranial pressure, such as torpor, intense optic neuritis and baldness. The primary growth may be overlooked, in some cases it could not be detected even though the regions were especially examined for it by palpation.

Fesenmaier<sup>6</sup> stated that in some cases pain in the abdomen, leading to the discovery of a palpable mass, may be the initial symptom, or, more commonly, swelling of the eyelids and protrusion of the eyes may attract the attention of the parents. Protrusion of one or both eyeball may be so extreme as to cause necrosis.

*Microscopic Pathology*—Smears made by Kato and Wachter from materials aspirated from both the marrow of the sternum and a cervical lymph node contained clusters of typical slightly basophilic cells, with relatively large hyperchromatic nuclei and fluid-like cytoplasm, which was usually scant.

Such cells, when later associated with the malignant cells similarly demonstrated in the tumor, were identified as metastatic sympathicoblasts or neuroblasts from the primary focus in the adrenal glands. Similar cells and groups of cells, often with two or three nuclei and of larger dimensions, were also observed in the imprint preparations made from the cut surface of the metastatic nodule in the skull.

No typical rosette formation of the pathologic cells was seen in any of the preparations studied, instead, there were seen the bonelike aggregations of cells described more typically as mosaic patterns.

For this reason, the general configuration of cell clusters characterizing this type of neoplasm should be referred to as "pseudorosettes," or, preferably, "mosaics."

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<sup>6</sup> Fesenmaier, O. B. Sympathetic Neuroblastoma, *Minnesota Med* 23:244, 1940.



Fig 3—*A*, microscopic appearance of cells of a neuroblastoma invading normal tissue, *B*, magnification of the tumor cells shown in *A*

*Diagnosis*—The diagnosis is based on (1) the age of patient, (2) the blood picture, (3) the presence of a palpable mass in the abdomen and (4) the observation of proptosis with orbital metastases

#### DIFFERENTIAL DIAGNOSIS

The clinical characteristics of tumor of the adrenal cortex are hypotism, pubertas precox and, frequently, an increasing blood pressure. Wilms's tumor usually occurs in children over 2 years of age and responds to irradiation. The tumor is frequently palpable. A pyelogram usually aids in the diagnosis. Hematuria occurs sooner or later. Involvement of the bone is rare, but when present the pelvis is the most likely site. Ascites is more likely to occur with lymphosarcoma than with other types. The superficial lymph nodes are often involved. They can be removed for biopsy. The malignant growth responds well to irradiation. Ovarian tumors are rare in children. The large tumors are frequently movable, they grow out of the pelvis. Bimanual examination is of diagnostic aid. In cases of tumors which are twisted on the pedicle, the picture is that of an acute abdominal condition with leukocytosis. In cases of leukemia, the general picture resembles that of a neuroblastoma of the adrenal gland. Repeated studies of the blood and bone marrow punctures should ultimately confirm the diagnosis. The patient with chloroma is usually older. The associated clinical features are those of leukemia. It must be borne in mind that the osseous changes of lymphatic leukemia may resemble greatly those of neuroblastoma of the adrenal cortex. The child with Hand-Schüller-Christian disease is usually older. The splenic enlargement is more pronounced. Studies of the blood lipids should be helpful. Roentgenologic study shows large circular defects in the skull. Ewing's sarcoma occurs late in childhood. Roentgenograms show an onion arrangement of the layers in the periosteal reaction. Occasionally the possibility of rheumatic fever must be eliminated. However, this should be done with ease when the entire picture is considered. Probably the greatest difficulty occurs in differentiation of neuroblastoma of the adrenal gland from lymphosarcoma, acute leukemia and chloroleukemia.

#### TREATMENT

Treatment up to this time has proved almost entirely ineffective. Irradiation produces a slight temporary response, while surgical intervention is usually followed by death within a short period. It must be mentioned, however, that a case was reported by Lehman<sup>7</sup> in which operation was performed in 1916 and the patient was still living and well in 1931, fifteen years later.

<sup>7</sup> Lehman, E. P. Adrenal Neuroblastoma in Infancy—Fifteen Year Survival. *Ann Surg* 95 473, 1932.

## SUMMARY

1 Proptosis of one or both eyes due to neuroblastoma of the adrenal cortex is seen almost entirely in very young infants, especially boys

2 This condition is highly malignant, and death occurs usually within three months after appearance of the first sign

3 The prognosis is bad, and up to the present treatment has been of no avail

4 Neuroblastoma of the adrenal cortex must always be considered in the cases of young male children when pain in the bone, bulging of the eyeball and an abdominal mass are present

Dr A C Snell Jr, of Rochester, N Y, Dr C E Iliff, of Baltimore, and Dr Paul Van Natta, of Washington, D C, assisted in the preparation of this paper

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# INFECTION OF THE HUMAN EYE WITH CRYPTOCOCCUS NEOFORMANS (TORULA HISTOLYTICA, CRYPTOCOCCUS HOMINIS)

A Clinical and Experimental Study with a New Diagnostic Method

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AND

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SAN FRANCISCO

SINCE slightly more than 100 cases of infection with *Cryptococcus neoformans* (*Torula histolytica*, *Cryptococcus hominis*) have been reported in the literature up to the present time, the disease should no longer be considered rare. The clinical, histopathologic and mycologic features have been adequately reviewed by Stoddard and Cutler,<sup>1</sup> Freeman,<sup>2</sup> Binford,<sup>3</sup> Dodge,<sup>4</sup> Benham<sup>5</sup> and Cox and Tolhurst.<sup>6</sup> Although a variety of ocular complications, including photophobia, diplopia, ptosis, rigidity of the pupils, amblyopia, strabismus, aniseikonia, nystagmus, neuroretinitis, papilledema, retinal hemorrhages, primary optic nerve atrophy and ophthalmoplegia, have been observed with a

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This study was aided by a grant from the Columbia Foundation of California

A preliminary report on this study appeared in Federation Proceedings (4:151, 1945)

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1 Stoddard, J L, and Cutler, E C. *Torula* Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916

2 (a) Freeman, W. *Torula* Infection of the Nervous System, *Jahrb f Psychol u Neurol* **43** 236, 1931. (b) Freeman, W, and Weidman, F D. Cystic Blastomycosis of the Cerebral Gray Matter, Caused by *Torula histolytica*, Stoddard and Cutler, *Arch Neurol & Psychiat* **9** 589 (May) 1923. (c) Freeman, W. *Torula* Meningo-Encephalitis, *Tr Am Neurol A* **56** 203, 1930

3 Binford, C H. *Torulosis* of the Central Nervous System, *Am J Clin Path* **11** 242, 1941

4 Dodge, C W. *Medical Mycology Fungous Diseases of Men and Other Mammals*, St Louis, C V Mosby Company, 1935, p 333

5 Benham, R W. *Cryptococci Their Identification by Morphology and by Serology*, *J Infect Dis* **57** 255, 1935

6 Cox, L B, and Tolhurst, J C. *Human Torulosis A Clinical, Pathological and Microbiological Study with a Report of Thirteen Cases*, Melbourne, Melbourne University Press, 1946



fair degree of regularity in this disease (Bettin<sup>7</sup>, Freeman<sup>2a</sup>, Holt<sup>8</sup>, Marshall and Teed<sup>9</sup>, Watts<sup>10</sup>, Reeves, Butt and Hammack<sup>11</sup>, Wade and Stevenson,<sup>12</sup> and others), few ophthalmologists have had the opportunity to make the diagnosis<sup>13</sup>, and only one communication dealing with an orbital infection due to *C. neoformans* has appeared in the literature<sup>14</sup>

We present the following interesting history of a patient whose initial symptoms related to poor vision and who immediately consulted three ophthalmologists in succession. The diagnosis, however, was not suspected, even after one eye had become blind and was enucleated. A culture of *C. neoformans* which we isolated from the remaining eye during the life of the patient was injected into the anterior chamber of rabbit eyes and this procedure led to the development of a new diagnostic test. The case also afforded the opportunity to observe, for the first time, the early histopathologic changes which occur in this disease.

#### REPORT OF A CASE

P. A., an Italian aged 56, consulted an ophthalmologist in July 1943 because of failing vision in the right eye. He was referred to another ophthalmologist, who made the diagnosis of a "cystic growth" in this eye. In August 1943 enucleation was performed by the first ophthalmologist, unfortunately, the contents of the eyeball were discarded, and only the choroid and cornea were sectioned.

The pathologic report reads as follows: "The specimen submitted is an eye which had previously been sectioned and the contents of both chambers evacuated. The globe was collapsed, and it had been fixed in dilute solution of formaldehyde U. S. P. in this state. Macroscopic examination failed to reveal any abnormalities. Microscopic examination showed areas of infiltration with small groups of lymphocytes and plasma cells, but no evidence of tumor. The diagnosis was that of an inflammatory process."

In the light of subsequent observations, fragments of tissue from the right eye were carefully reexamined, but no evidence of cryptococci was apparent. Our

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7 Bettin, M. E. Report of a Case of *Torula* Infection, California & West Med **22** 98, 1924.

8 Holt, R. A. The Identification of *Blastomyces Histolytica* in Three Infections of the Nervous System, J. Lab. & Clin. Med. **27** 58, 1941.

9 Marshall, M., and Teed, R. W. *Torula Histolytica* Meningoencephalitis, J. A. M. A. **120** 527 (Oct. 17) 1942.

10 Watts, J. W. *Torula* Infection, Am. J. Path. **8** 167, 1932.

11 Reeves, D. L., Butt, E. M., and Hammack, R. W. *Torula* Infection of the Lungs and Central Nervous System. Report of Six Cases with Three Autopsies, Arch. Int. Med. **68** 57 (July) 1941.

12 Wade, L. J., and Stevenson, L. D. *Torula* Infection, Yale J. Biol. & Med. **13** 467, 1940-1941.

13 Cohen, M. Binocular Papilledema in a Case of *Torulosis* Associated with Hodgkin's Disease, Arch. Ophth. **32** 477 (Dec.) 1944.

14 Gill, W. D. *Torula* Mycosis in Man with Special Reference to Involvement of the Upper Respiratory Tract, with Case Report, Tr. Am. Laryng., Rhin. & Otol. Soc. **40** 247, 1934.

report was as follows. There were two defects in the sclera, which were lined with material undergoing coagulation necrosis. One defect penetrated the sclera, the other did not. They appeared to be at the site of cauterization. The cornea showed an old ulceration, the epithelium at the edge of the ulcer being hyperplastic and forming a rounded margin. Sections containing retina showed it to be the site of a chronic inflammatory process, as manifested by the presence of lymphocytes and macrophages. Some of the macrophages contained melanotic pigment. At the ora serrata the choroidal pigment had migrated into the sclera. The choroid was thickened and contained lymphocytes.

After enucleation, the patient returned to work but was unable to continue with his usual activities because a defect had developed in the field of vision of the remaining eye. Shortly thereafter he had a mental upset and was taken to a sanatorium, where he stayed from October 15 to November 7. His mental condition improved, but the vision in his left eye became progressively worse, until, in November 1943, he could merely count fingers at 10 inches (30 cm).

*Past History*—The patient had been in an automobile accident two years previously but gave no history of fracture or of unconsciousness. About ten years prior to hospitalization he noticed a swelling on the dorsum of his hand close to his thumb, this did not increase in size and was not painful.

*Physical Examination*—The patient was well developed and well nourished. He was in bed and responded sluggishly to questioning. The head was of normal contour. The right eye was replaced by a prosthesis, the pupil of the left eye was fixed. The conjunctiva was slightly injected. Multiple fine deposits were present on the posterior surface of the cornea, aqueous floaters were graded 4 plus, fine deposits were noted on the anterior capsule of the lens. Vitreous floaters, grade 4 plus, were present. A large retinal detachment extended from 6 to 11 o'clock, it was not wavy and did not fluctuate but had the appearance of a cystic mass. Transillumination was even and revealed nothing abnormal. Hearing was essentially normal.

The lungs appeared clear on percussion and auscultation. The heart sounds were of good quality, the rhythm was regular, there were no murmurs. The blood pressure was 128 systolic and 80 diastolic. The abdomen was not remarkable. The extremities were normal except for a mass over the dorsum of the right hand close to the thumb, this tumor was freely movable, about the size of a peach and of moderate consistency. The neurologic status was essentially normal. The mental state was not studied.

*Diagnosis*—The right eye was replaced by a prosthesis. The left eye presented a retinal detachment, possible cyst of the retina and uveitis, a lipoma was present on the dorsum of the right hand.

*Operation and Subsequent Course*—On November 23 a trephine opening was made in the sclera (but not in the choroid) 12 mm from the limbus and inferior to the medial rectus muscle. A heavy, viscid, brownish fluid drained through the opening. The fluid was cultured, and a pure growth of *C. neoformans* (T histolytica, C hominis) was obtained. On December 3 a second trephination of the sclera was performed about 12 mm from the limbus at 7 o'clock. An 18 gage needle was inserted into the subretinal space, and about 1 cc of a heavy, viscid, gelatinous fluid and 2 cc of a yellowish fluid were aspirated. Cultures of this material revealed a cryptococcus similar to that obtained after the first operation.

The family reported that the patient died in 1946. There was no autopsy.

## LABORATORY INVESTIGATIONS

The fluid obtained by trephining the sclera was cultured on corn meal agar, blood agar and thioglycollate broth. A pure culture of a yeastlike organism developed, which after inoculation into mice was identified as *C. neoformans* (*T. histolytica* or *C. hominis*), group III (Benham<sup>5</sup>). Subcultures were sent to Dr. Morris Moore, Barnard Free Skin and Cancer Hospital, St. Louis, and to Dr. Rhoda W. Benham, Medical Center, New York, both of whom confirmed our observations.

## CULTURAL CHARACTERISTICS

The colonies of cryptococci were creamy white, becoming tan with age, they were fairly moist, nonfriable, finely granular, opaque and umbonate, with an

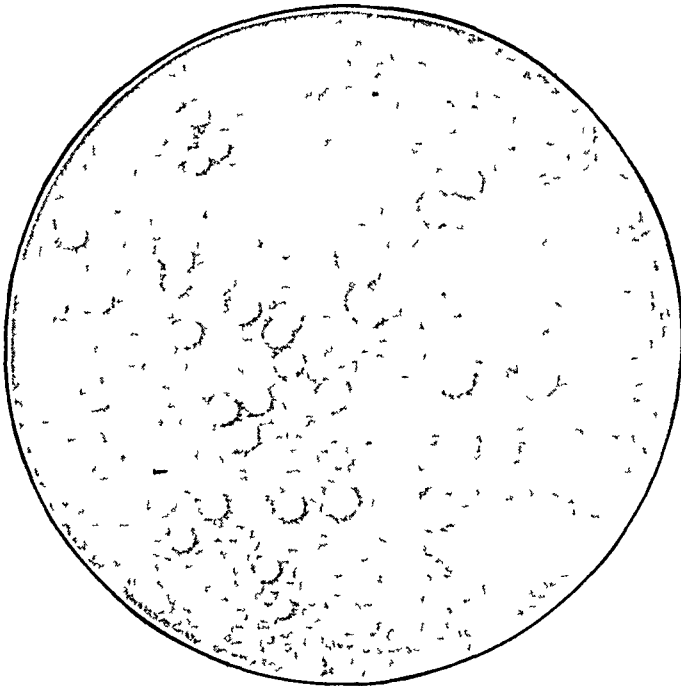


Fig. 1—Colonies of *Cryptococcus neoformans* on a corn meal agar plate

entire periphery (fig. 1). There was no fermentation of dextrose, maltose, levulose, sucrose, lactose, galactose or mannite after one week's observation. Maltose and sucrose showed slight acid formation after four weeks' incubation. There was pellicle formation in milk. No liquefaction of gelatin was seen during three months' observation, and there was no evidence of mycelial formation. Multiplication occurred by budding only. Ascospore formation was not observed.

## PATHOGENICITY FOR MICE

*Intraperitoneal Route*—Two mice were inoculated intra-abdominally with cultures of cryptococci. One died nineteen days later, the other was moribund and was killed. Cryptococci were recovered in pure culture from the brain and genitalia of both animals. Dr. Morris Moore also inoculated several mice intraperitoneally with our strain. They died four to eight days after injection. The organisms were demonstrable in stained section of various viscera, including the pancreas.

*Intravenous Route*—On Dec 28, 1943, 3 mice were inoculated intravenously with doses of 0.25 cc of a suspension of a turbidity equal to that of the no. 1 tube of a McFarland nephelometer. Five days later one animal was moving about in circles and had a tumor-like swelling in the occiput. It died forty-one days after injection. Autopsy revealed that the brain was soft and gelatinous. The organism was cultivated from the brain, liver and spleen and from the gelatinous tumor on the occiput, which had eroded through the skull. The second mouse was found dead on the twentieth day, and the third on the forty-first day, after injection. Cryptococci were isolated from the viscera of each animal.

#### PATHOGENICITY FOR RABBITS

*Intraocular Route*—Eight rabbits received injections of cultures into the anterior chamber. The technic was carefully controlled, so as not to injure the iris.<sup>15</sup> Anesthesia was induced by intravenously administered pentobarbital, supplemented by ether in order to prevent the animal from struggling. The dose was 0.1 cc of a twenty-four hour culture which was made up to a turbidity equal to that of the no. 1 tube of a McFarland nephelometer and was further diluted to 1:100 with buffered saline solution. Only one eye of an animal was inoculated, the second serving as a control. Enucleations for the purpose of histologic study were made at intervals of seventeen and one hundred and twenty days after injection.

*Animals Killed for Observation After Seventeen Days* The results with 4 rabbits were essentially similar, and the protocol of only 1 will be cited.

**RABBIT 677** Injection into the left eye was made on Dec 28, 1943. No noteworthy symptoms appeared until six days later, when there was severe inflammation of the upper palpebral conjunctiva and the entire bulbar conjunctiva, with moderate iritis. The cornea was clear. Four days later there was severe congestion of the sclera and lids and two tiny opaque spots were seen in the center of the pupillary area. The cornea had a faint, milky opacity. Seventeen days after injection the lids were red and showed a slight discharge. The vessels of the sclera were congested, the cornea had a milky opacity, and it was difficult to see the markings of the iris. The eye was now enucleated for study.

*Histopathologic report* A slight exudate of polymorphonuclear leukocytes and some monocytes was observed along the periphery of the cornea, with a minute area of acute necrosis. Along the anterior surface of the iris and the posterior surface of the cornea there was a delicate festoon of rosettes (fig. 2), in the center of which was a cryptococcus (torula). Surrounding the organism was a single row of cells composed of both polymorphonuclear leukocytes and monocytes. Where the rosette was detached and lay free in the anterior chamber, the single row of host cells surrounding the organism was conspicuous and suggested that the cells adhered to the gelatinous capsule. The reaction was greatest at that part of the anterior chamber which was opposite the point of inoculation. Here the monocytes had evolved into macrophages and in a few instances had two to three nuclei. Occasionally an engulfed organism was seen inside a macrophage. The cryptococci were from 5 to 10 microns in diameter, possessed a thick, mucoid capsule, were

<sup>15</sup> Benjamin, L., Jr., Belt, E., and Krichevsky, B. Total Prostatectomy in the Rabbit and Intra-Ocular Transplantation of Prostatic Tissue, *J. Urol.* **44**, 109, 1940. Gilbert, W., and Plaut, F. Ueber Kammerwasseruntersuchung. I, *Arch. f. Augenh.* **90**, 1, 1921.

sometimes apiculate and showed definite budding (fig 3) The organisms and their buds were sometimes a clear, pale green and at other times contained a coarse, dark brown pigment The iris and ciliary body were edematous (fig 4) There was no evidence of penetration of the cryptococci into the tissues, although the stroma of the ciliary body was loose and vascular The posterior chamber was normal

Animals Killed for Observation After Four Months The results for the 2 animals in this series were similar

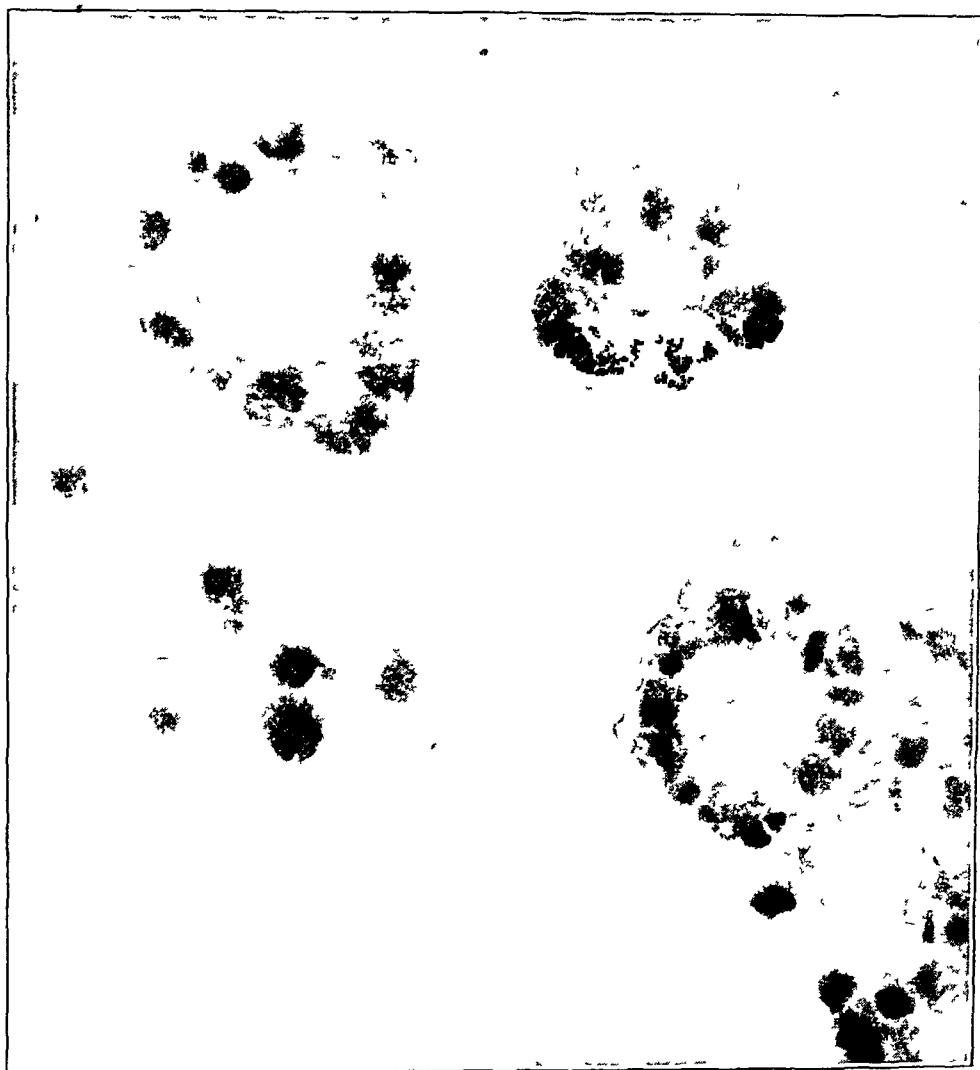


Fig 2—Section of rabbit eye (rabbit 676) enucleated one week after injection of cryptococci into the anterior chamber, showing rosette formation

RABBIT 675 Inoculation was made on December 16

Twelfth day Inflammation of the palpebral and bulbar conjunctivas, mild *iritis* and slight cloudiness of the cornea were noted

Eighteenth day The eye was closed, a thick, mucopurulent exudate was seen in the inner canthus, the eyelids were red and sticky, the cornea was slightly opaque and the bulbar and palpebral conjunctivas were congested

Twentieth day The upper palpebral conjunctiva was slightly congested, the lids were normal, the bulbar conjunctiva was slightly congested, a hypopyon extended from 5 to 7 30 o'clock, the cornea was slightly opaque, the iris was nearly normal

Twenty-seventh day The palpebral and bulbar conjunctivas were congested, there was a mucopurulent discharge, the cornea had a milky opacity, the iris was difficult to see, the hypopyon was still present, exophthalmos was present

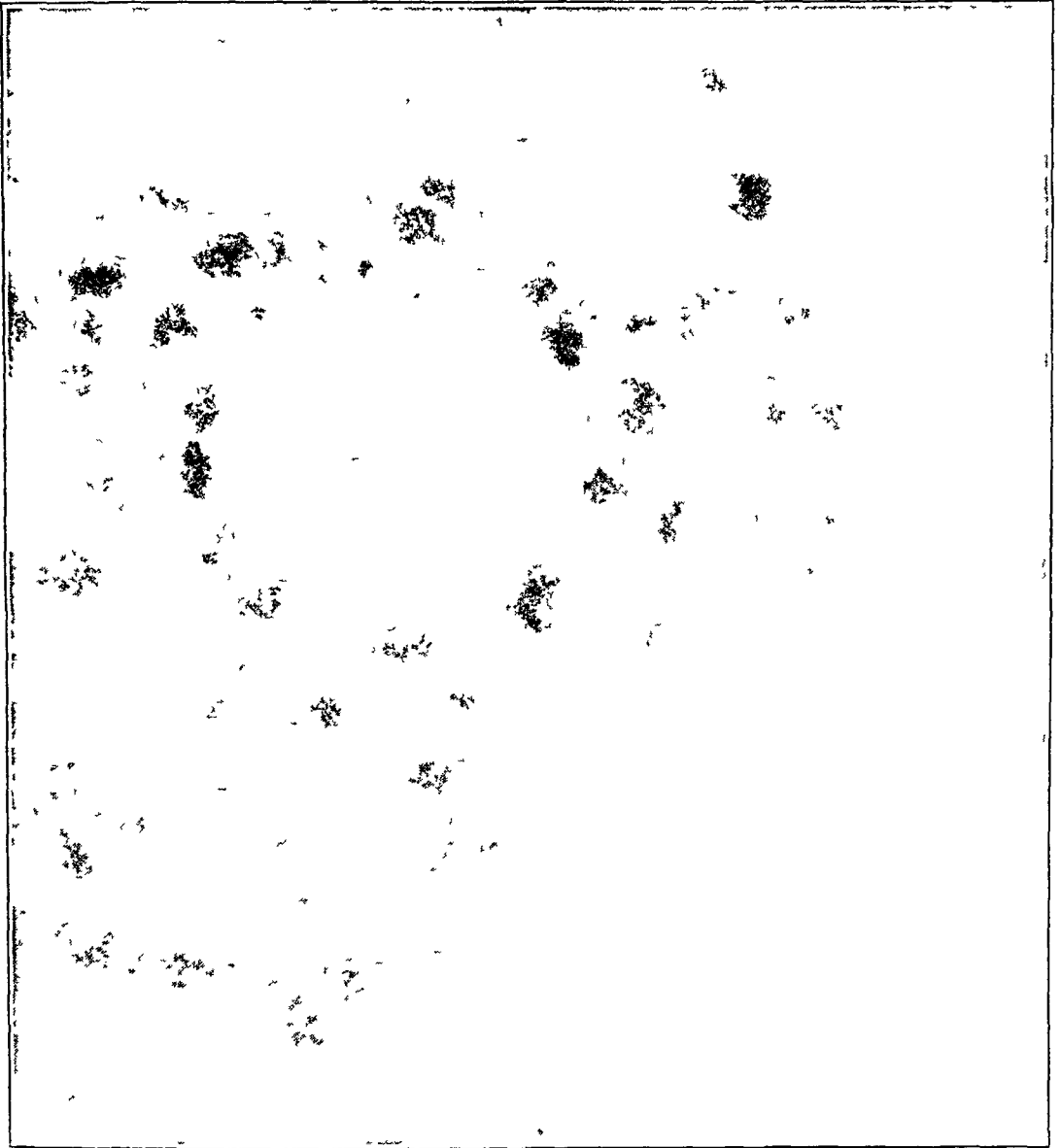


Fig 3—Budding organisms, showing mucoid capsule, surrounded by leukocytes and macrophages, and rosette formation (from the same section as that illustrated in figure 2)

Forty-first day The rabbit appeared groggy and was very quiet in the cage, the eye was held shut, the conjunctiva was congested and glassy, there was no discharge, the iris was obliterated by an opaque cornea, a hypopyon was present, the pupillary area was opaque

Forty-eighth day A heavy, narrow, creamy band lay apparently on the posterior surface of the cornea and extended toward the iris a half-moon-shaped

opacity appeared like a dense, half-ringed synechia at the margin of the iris and adhered to the capsule of the lens, the pupil was small and fixed, the fundus could not be seen, many superficial vessels invaded the cornea at the limbus, the iris was hyperemic

Fifty-second day Observation with the slit lamp (Dr Frank H Rodin) revealed dense vascularization of the cornea, beginning at the limbus and occupying the whole cornea except for the central pupillary area, a synechia was present at the point where the iris adhered to the lens

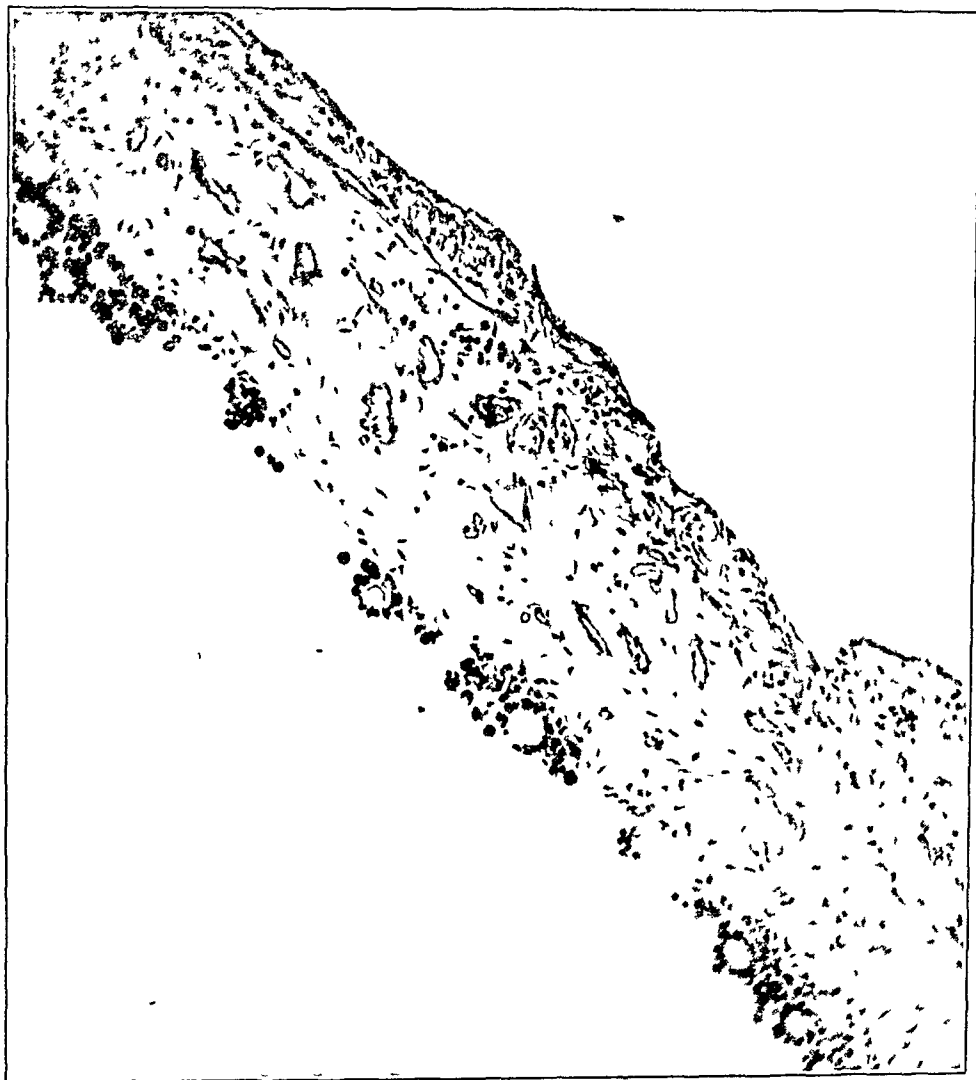


Fig 4—Low power magnification of the iris, showing that the cryptococci have not penetrated into tissues of the iris, rosette formation

Gross pathologic appearance after enucleation (one hundred and twentieth day) The inferior part of the anterior chamber was opaque and creamy, with somewhat nodular conformation. There were small, vesicular blebs over the inferior part of the cornea and the sclera. It was not determined whether these lesions were cysts or emphysematous blebs. A pannus was present over the entire circumference of the cornea but was densest in the inferior part. In vivo the pannus was most intense in the superior part of the cornea. The cornea was opaque, and the pupil was not all distinguishable.

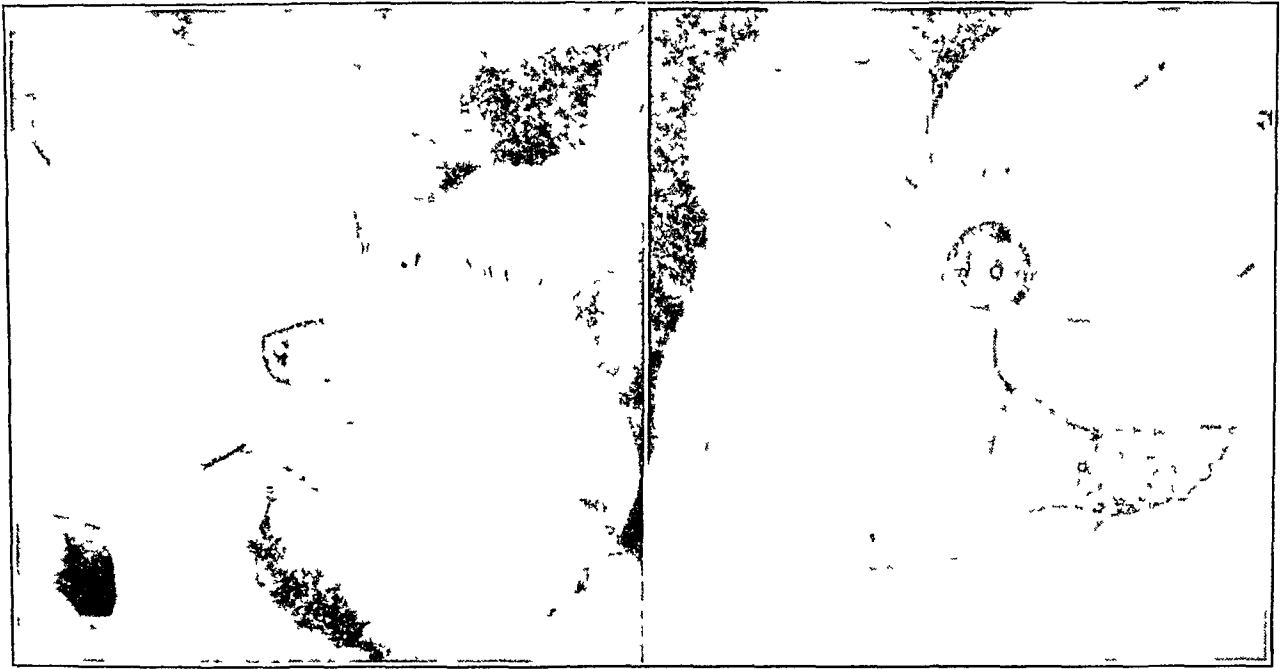


Fig 5—Contrasting appearance of the normal (left) and the inoculated (right) eye of a rabbit twelve days after intraocular injection with cryptococci

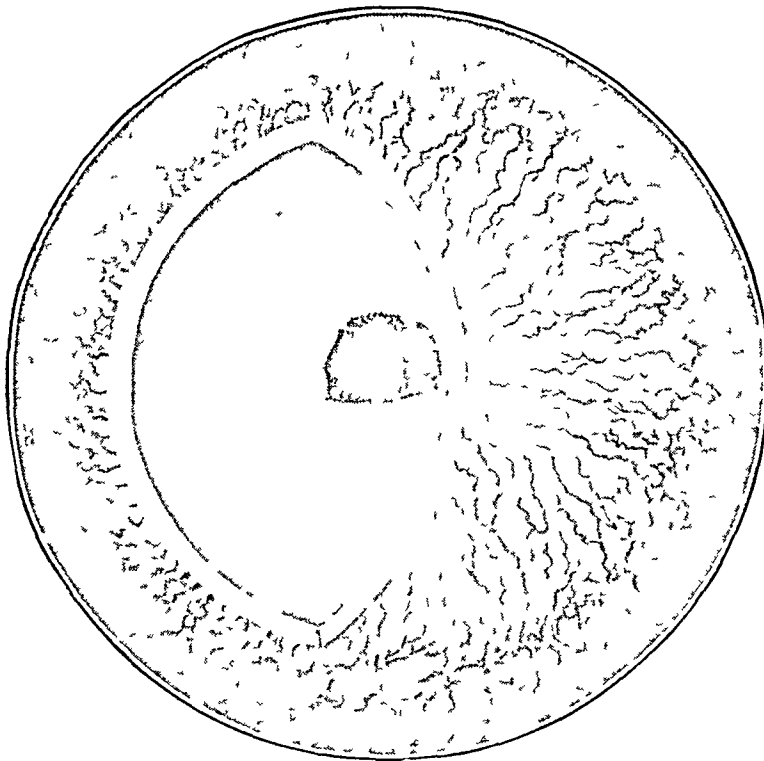


Fig 6—Appearance of a rabbit eye three weeks after injection into the anterior chamber of *Cryptococcus neoformans*



**Histologic report** Left eye The iris was adherent to the cornea, which was scarred and vascularized. In the anterior chamber a dense neutrophilic exudate surrounded the calcifying cryptococci. Another focus contained rings with a few shells of organisms. In the center of a circumscribed abscess were many neutrophils with an outer ring of macrophages and lymphocytes. The macrophages were large and had ingested much detritus. A few abortive giant cells were seen.

**Right eye** The eye was normal.

**Other Routes of Infection**—Three other routes of inoculation were used in rabbits, with negative results. When injections were made subconjunctivally or intradermally, there was only a local bleb or a small nodule with slight inflammation, which persisted for several days. Intravenous injection of 30 cc into 2 rabbits elicited no symptoms during a period of observation of four and one-half months. These animals looked well when killed and showed no evidence of infection.

#### COMMENT

The present case of infection of the eye with *C. neoformans* (*T. histolytica*, *C. hominis*) is the second such instance on record. Other communications dealing with localized lesions due to this organism have been published. Among the sites of infection are the knee,<sup>16</sup> nasopharynx,<sup>17</sup> pelvis,<sup>18</sup> spine,<sup>19</sup> skin<sup>20</sup> and rectum.<sup>21</sup> It is likely that all cases of such lesions represent localized manifestations of systematic mycoses.

It was not possible to establish the portal of entry in our case. Some authors have suggested the respiratory tract. It must be pointed out, however, that Fazakas<sup>22</sup> found cryptococci repeatedly in both the normal and the diseased conjunctiva, and this surface might have served as the avenue of infection. Since the identification of *C. neoformans* depends largely on the demonstration of its pathogenicity, the choice of a suitable susceptible animal becomes a matter of considerable importance. There has been much discussion of this subject in the literature.

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16 Kessel, J. F., and Hoetzwart, F. Experimental Studies with *Torula* from a Knee Infection, *Am J Trop Med* **15** 467, 1935.

17 Jones, E. L. *Torula* Infection of the Nasopharynx, *South M J* **20** 120, 1927.

18 McGehee, J. L., and Michelson, I. D. *Torula* Infection in Man, *Surg, Gynec & Obst* **42** 803, 1926, cited by Jones<sup>17</sup>.

19 Brewer, G. E., and Wood, F. C. Blastomycosis of the Spine, *Ann Surg* **48** 889, 1908, cited by Reeves, Butt and Hammack<sup>11</sup>.

20 Mook, H. W., and Moore, M. Cutaneous Torulosis, *Arch Dermat & Syph* **33** 951 (June) 1936. Wile, U. J. Cutaneous Torulosis, *ibid* **31** 58 (Jan) 1935.

21 Allen, V. K., and Lowbeer, L. Rectal Ulcers with Perirectal Fistula as Port of Entrance for *Torula* Encephalitis, *South M J* **38** 565, 1945.

22 Fazakas, A. Ueber die Schimmelpilze des gesunden und kranken Auges, *Arch f Ophth* **138** 416, 1938.

As pointed out by Gray,<sup>23</sup> Kessel,<sup>16</sup> Longmire and Goodwin,<sup>24</sup> Crone, DeGroat and Wahlin<sup>25</sup> and Freeman,<sup>2</sup> rabbits, when infected, show irregular results or are entirely resistant. By injecting the organisms into the anterior chamber of these animals, we produced severe keratitis, iritis, pannus and total blindness. The use of the intraocular route has the advantage that the lesion can be seen grossly within a week after infection and reaches its full development at the end of fourteen to seventeen days.

The histologic features of these early lesions are characteristic and differ from those seen late either in the experimental or in the natural disease. Thus, along the anterior surface of the iris and the posterior surface of the cornea we observed a delicate festoon of rosettes, in the center of which was a cryptococcus. Surrounding the organism was a single row of cells, composed of both polymorphonuclear leukocytes and monocytes. This rosette formation has not previously been described. The only observation in the literature which resembles it is that of Rappaport and Kaplan,<sup>26</sup> who, when referring to a metastatic cutaneous lesion due to the torula, stated

Under the intact skin at one margin of the ulcer there was a marked, diffuse infiltration of the yeastlike organisms in a granular debris. Some round cells and many fibroblasts were present. The latter in some places revealed a peculiar arrangement, three to four of the cells surrounding one organism about which there was a clear space, giving the appearance of an organism within a capillary [no illustrations]

The reaction previously described as a rosette formation is interpreted as due to the opportunity to observe advantageously the exudative response of the tissues to cryptococci in the initially acellular space of the anterior chamber of the eye and in the early stage of infection. The conventional description of the late stages of torulosis is that of a chronic granuloma with caseous areas resembling tuberculosis. The characteristic features include the formation of giant cells and the absence of polymorphonuclear leukocytes. This picture may be explained on the basis of the advanced age of the lesions. Thus Stoddard and Cutler<sup>1</sup> described the lesion in the liver of a rabbit autopsied three weeks after intraperitoneal inoculation

a large area with central caseation, surrounded by epithelioid cells, then a zone of thick infiltration with lymphoid cells, containing many eosino-

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23 Gray, F. C. Two Cases of Torula Meningitis, with Special Reference to Laboratory Findings, *South African M J* **14**:65, 1940

24 Longmire, W. P., Jr., and Goodwin, T. C. Generalized Torula Infection, *Bull. Johns Hopkins Hosp.* **64**:22, 1939

25 Crone, J. T., DeGroat, A. F., and Wahlin, J. G. Torula Infection, *Am J Path.* **13**:863, 1937

26 Rappaport, B. Z., and Kaplan, B. Generalized Torula Mycosis, *Arch. Path.* **1**:720 (May) 1926

philic cells, with a slight surrounding connective tissue band [In the brain, there occurs] a chronic meningitis in which definite torula organisms are found. The cells consist chiefly of large mononuclear cells and sometimes contain organisms. There are moderate numbers of plasma cells, but no polynuclear cells. The organisms are scarce and show much degeneration. The large phagocystic mononuclear cells are filled with hyaline droplets or vacuoles. The cortex near the lesion has a slight increase in glia tissue, with spider glia cells. In the cortex are focal lesions consisting of accumulations of mononuclear, lymphoid and plasma cells.

These authors concluded that the torula does not attract polymorphonuclear leukocytes at any stage and that its pathogenicity for rabbits is slight.

Freeman<sup>20</sup> described the histopathologic characteristics of human torular meningoencephalitis as follows:

Microscopically, the diffuse meningitis is characterized by marked proliferation of endothelial cells and the formation of new fibrous tissue, together with infiltration by lymphocytes and plasma cells, but practically never by polymorphonuclear leukocytes, and by the occurrence of a moderate number of giant cells, usually with centrally placed nuclei less often of the Langhans type.

In general, as shown by Crone, DeGroat and Wahlin,<sup>25</sup> the degree and character of the inflammatory response to infection with *C. neoformans* depend on the local supply of cells capable of being mobilized as macrophages in any given organ or tissue. Our data emphasize the importance of considering the age of the lesion.

#### SUMMARY

A case of infection of the human eye with *C. neoformans* (*T. histolytica*, *C. hominis*) is reported. The clinical diagnosis was "possible cyst of the retina with retinal detachment and uveitis." The sclera was trephined, and material obtained for culture showed the presence of this yeastlike organism.

By injection of the culture into the anterior chamber of rabbit eyes, it was possible to observe pathologic changes as early as the fifth to the seventh day. These lesions were fairly well established by the seventeenth day. The inferior part of the anterior chamber became opaque; there was plastic iritis, and a pannus developed on the surface of the cornea.

Histologically, there was a slight exudate consisting of polymorphonuclear cells and monocytes along the periphery of the cornea. Along the anterior surface of the iris and the posterior surface of the cornea there was a delicate festoon of rosettes. In the center of each rosette there was a cryptococcus, surrounded by a single row of polymorphonuclear cells and monocytes. The organisms were seen to be engulfed inside macrophages. The early stages of infection in the rabbit eye are there-

foie characterized by the formation of rosettes, which suggest actual agglutination on to the mucous capsule of the cryptococcus, the absence of invasion, and the presence of both acute and chronic exudative responses

Since in most cases of human infection with *C. neoformans* the diagnosis has been made either post mortem or late in the disease, after several weeks or months of illness, it is hoped that this new method of intraocular injection of rabbits, together with the description of the early histologic reaction, may contribute to an earlier diagnosis of this fatal disease

The late Dr Martin I Green, of Greens' Eye Hospital, San Francisco, furnished the medical history, and Dr Arthur Haim referred the patient to us for investigation

Jewish Hospital, Philadelphia (Dr Weiss)

Departments of Pathology (Dr Perry) and Bacteriology (Miss Shevky) of University of California Medical School, San Francisco

# CONTROVERSIAL POINTS IN PENICILLIN THERAPY OF OCULAR DISEASES

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## OUTLINE OF STUDY

- I Parenteral use of penicillin
  - A Passage of penicillin across blood-aqueous barrier
  - B Penicillin level in ocular and other body fluids after ligation of renal vessels
  - C Passage of penicillin from blood into aqueous and vitreous in ocular inflammation
- II Surface applications of penicillin
  - A Solutions and ointments
  - B Iontophoretic introduction of penicillin
    - 1 Conductivity of sodium penicillin
    - 2 Influence of change in hydrogen ion concentration at cathode on activity of penicillin
    - 3 Factors acting on passage of penicillin through cornea during iontophoresis
      - (a) Flow of electric current from cathode
      - (b) Changes in hydrogen ion concentration of bathing fluid
      - (c) Polarity of terminal
      - (d) Tonicity of penicillin solution
    - 4 Value of high drug levels in aqueous after corneal iontophoresis or similar procedures
    - 5 Palpebral iontophoresis
- III Local injections of penicillin
  - A Under conjunctiva
  - B Into anterior chamber
  - C Into lens
  - D Into vitreous
    - 1 Crystalline penicillin
    - 2 Penicillin and antitoxin
- IV General conclusions

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Presented as a candidate's thesis in partial fulfilment of the requirements for membership in the American Ophthalmological Society, 1947

From the Department of Ophthalmology of Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital

The literature on the use of penicillin in ophthalmology has grown extensively in the last few years and has been summarized in several reviews. It is the purpose of this paper to study certain contradictions in, and unsettled questions concerned with, various types of ocular penicillin therapy rather than to complete the list of pertinent publications.

## I PARENTERAL USE OF PENICILLIN IN OPHTHALMOLOGY

Most investigators agree that parenteral penicillin therapy in ophthalmology should be limited to severe infections of the lids, conjunctiva and orbit. The opinion is based less on clinical observations than on early experimental data which demonstrated that the intraocular fluids of normal human eyes and of normal eyes of experimental animals showed little or no antibacterial activity after systemic use of penicillin in common doses<sup>1</sup>. However, extracts from other parts of the normal eye of rabbits, such as the sclera, conjunctiva and choroid-retina, contained more penicillin<sup>1b, c</sup>. Paracentesis<sup>2</sup> and experimentally induced intraocular vasodilatation<sup>3</sup> brought about an increase in the drug level in the aqueous after parenteral injection of penicillin, but even then its height compared unfavorably with that obtained with local procedures. The results of these studies on distribution of penicillin in the normal eye explain the preference for topical methods, since the assumption that better therapeutic effects are obtained with higher drug levels has been applied to penicillin.

### A PASSAGE OF PENICILLIN ACROSS THE NORMAL BLOOD-AQUEOUS BARRIER

The poor penetration of penicillin into the intraocular fluids and ocular tissues from the blood is similar to that reported for cerebrospinal fluid and brain tissue, although the blood-brain barrier seems to interfere with the transport of the drug into the spinal fluid more than the blood-aqueous barrier in the transfer of penicillin into the

1 (a) von Sallmann, L., and Meyer, K. Penetration of Penicillin into the Eye, *Arch Ophth* **31** 1 (Jan) 1944. (b) Struble, G. C., and Bellows, J. G. Studies on the Distribution of Penicillin in the Eye, *J. A. M. A.* **125** 685 (July 8) 1944. (c) Bellows, J. G. Penicillin Therapy in Ocular Infections, *Am J Ophth* **27** 1206 (Nov) 1944. (d) Leopold, I. H. Intravitreal Penetration of Penicillin and Penicillin Therapy of Infections of the Vitreous, *Arch Ophth* **33** 211 (March) 1945. (e) Rycroft, B. W. Penicillin and the Control of Deep Intraocular Infection, *Brit J Ophth* **29** 57 (Feb) 1945.

2 (a) von Sallmann and Meyer<sup>1a</sup>. (b) Struble and Bellows<sup>1b</sup>. (c) Town, A. E., and Hunt, M. E. Penicillin in the Aqueous Humor, *Am J Ophth* **29** 171 (Feb) 1946.

3 (a) Leopold<sup>1d</sup>. (b) Mann, I. Intraocular Use of Penicillin, *Brit J Ophth* **30** 134 (March) 1946.

ocular fluids McDermott and Nelson<sup>4</sup> enumerated three mechanisms which might account for the fact that only traces of penicillin are assayable in the spinal fluid after parenteral use of the compound (1) the binding of penicillin to nondiffusible components of serum, (2) the molecular structure of penicillin, which would make the compound unsuitable for the transport across the blood-spinal fluid barrier, and (3) rapid inactivation of penicillin by some constituent of nerve tissue or cerebrospinal fluid after the drug has passed the barrier On the basis of dialysis and diffusion experiments, these authors discarded the first mechanism, they could not investigate the second because of the limited knowledge concerning the molecular structure of penicillin at the time of their studies With regard to the third possibility, it is merely known that cerebrospinal fluid does not inactivate penicillin *in vitro*

Thus far, the problem of the transport of penicillin across the blood-aqueous barrier has not been studied A possible cause of the low penicillin content of the aqueous was revealed in the dialysis experiments of Chow and McKee,<sup>5</sup> which provided evidence that crystalline penicillin combines with human serum albumin, however, this mechanism could be considered a relatively minor factor Untenable is the theory of inactivation of the antibiotic by ocular fluids or tissues, because penicillin was not destroyed in either aqueous or ground ocular tissues which were stored in the refrigerator for a number of hours Nor does the gradient of the depletion curve of the aqueous indicate such a loss of potency Additional evidence was presented by recent experiments of this laboratory in which sodium penicillin in centrifuged vitreous fluid of normal rabbits did not lose its activity more rapidly than a solution of the antibiotic of equal strength in a phosphate buffer when exposed to temperatures of 2, 24 and 37 C for four hours

The scarcity of the types of pure penicillin prevented the study of the relation of their stereochemical structure to the transport across the blood-aqueous barrier The part which the components of this barrier play as possible obstacles to the transfer of penicillin was examined by using cyanide for the *in vivo* inhibition of the indophenol oxidase (cytochrome oxidase) in the ciliary epithelium

The work of Warburg<sup>6</sup> on the inhibition of the respiratory mechanism by low concentrations of cyanide was used by Seidel,<sup>7</sup> Schmelzer,<sup>8</sup>

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4 McDermott, W, and Nelson, R A Transfer of Penicillin into the Cerebrospinal Fluid Following Parenteral Administration, *Am J Syph, Gonorr & Ven Dis* **29** 403 (July) 1945

5 Chow, B F, and McKee, C M Interaction Between Crystalline Penicillin and Human Plasma Proteins, *Science* **101** 67 (Jan 19) 1945

6 Warburg, O H Ueber die katalytischen Wirkungen der lebendigen Substanz, Berlin, Julius Springer, 1928

Friedenwald and Stiehler,<sup>9</sup> Duke-Elder and others<sup>10</sup> as a basis for their various studies on the function of the blood-aqueous barrier. Cyanide solutions were injected into the vitreous (Seidel and Schmelzer), applied by a supravital technic on the excised ciliary body (Friedenwald and Stiehler) or added to the perfusion fluid for use on the isolated dog head (Duke-Elder). None of these experimental approaches was suitable for the current investigation. Pronounced changes in the intraocular pressure due to the injection of any fluid into the vitreous are generally followed by an unpredictable response of the intraocular vessels even when nonirritating solutions are used. Similar objections must be raised in regard to the perfusion experiments, as severe disturbances in the capillary permeability are usually observed in such preparations. The supravital technic of Friedenwald could not be applied, for the concentration of penicillin in the aqueous had to be determined after inhibiting the respiratory mechanism of the ciliary epithelium. A complete or partial suppression of the cyanide-sensitive system in this structure was therefore attempted *in vivo* with cyanide iontophoresis.

In preliminary experiments, measurements were made of the cyanide concentrations and the protein levels in the aqueous. The effect of the cell poison on the cytochrome oxidase of the ciliary epithelium of albino rabbits was then tested with the indophenol oxidase reaction. In subsequent series of experiments, the amount of penicillin which penetrated from blood to aqueous in the poisoned eyes was compared with that of variously treated control eyes. The inhibition of the cytochrome oxidase in the ciliary epithelium of the eyes treated with cyanide was again verified by the test for indophenol oxidase, and results were collated with those in the control eyes. The influence of the cyanide on the permeability of the intraocular vessels was deduced from the protein content of the aqueous.

*Technic of Preliminary Experiments*—For the iontophoretic induction of the cyanide into the anterior segment of the eye, the orifice of the applicator glass tube was widened at the lower end so that its rim fitted the region of the ora serrata. A 0.5 per cent solution of potassium cyanide adjusted to a  $p_H$  of 7 with phosphoric acid, or a solution of sodium cyanide of the same strength neutralized with hydro-

7 Seidel, E. Ueber die Gewebsatmung im Auge und ihre klinische Bedeutung, *Ber d deutsch ophth Gesellsch* **45** 14, 1925.

8 Schmelzer, H. Mikrochemische Reaktionen am Ziliarepithel, *Ber d deutsch ophth Gesellsch* **45** 259, 1925.

9 Friedenwald, J. S., and Stiehler, R. D. Circulation of the Aqueous. VII. A Mechanism of Secretion of the Intraocular Fluid, *Arch Ophth* **20**:761 (Nov.) 1938.

10 Duke-Elder, W. S., Quilliam, J. C., and Davson, H. Some Observations on the Present Position of Our Knowledge of the Intraocular Fluid, *Brit J Ophth* **24** 421 (Sept.) 1940.



chloric acid, was applied iontophoretically at 2 milliamperes for five minutes to the right eye of each rabbit in the series. The left eyes were treated in like manner with a 0.9 per cent solution of sodium chloride or with a phosphate buffer of  $p_H$  7. Other (control) eyes were subjected to histamine iontophoresis. The dihydrochloride salt in a concentration of 0.1 per cent was applied from the anode at 1 milliampere for two minutes. The amount of cyanide in the aqueous was examined at various intervals. Of the three methods of cyanide determination which were tested—the silver nitrate method of Brunswick,<sup>11</sup> the picric acid method of Smith<sup>12</sup> and the bromine method of Aldridge<sup>13</sup>—the last was found suitable for a quantitative spectrophotometric technique.<sup>14</sup>

Two-tenths cubic centimeter of aqueous was diluted with 1 cc of a 5 per cent solution of trichloroacetic acid and centrifuged. Five-tenths cubic centimeter of bromine water and 0.5 cc of a 15 per cent aqueous solution of sodium arsenate were added to 1 cc of the supernatant. One cubic centimeter of this solution (A) was mixed with 5 cc of freshly prepared solution (B), which consisted of 5 cc of the pyridine reagent (25 cc of pure redistilled pyridine and 2 cc of concentrated hydrochloric acid diluted to 100 cc) and 0.2 cc of a 2 per cent aqueous solution of benzidine hydrochloride. Ten minutes was allowed for development of color. The results were read against concurrent standards, which gave a straight line in a Coleman spectrophotometer set at a wavelength of 480 microns. One microgram of potassium or sodium cyanide per cubic centimeter could be determined. The protein in the aqueous was determined nephelometrically, as described in a previous article.

**Results**—An unneutralized solution of potassium or sodium cyanide (0.5 per cent) caused a diffuse alkali burn of the cornea when it was applied with the ionization method. The cornea later became scarred and vascularized. When the solution was adjusted to a  $p_H$  of 7 with phosphoric acid or with hydrochloric acid, a transient haziness of the epithelium and hyperemia of the pericorneal vessels and the vessels of the iris were noted. An average cyanide content of the aqueous of 43.41 micrograms per cubic centimeter was determined thirty minutes after iontophoresis. It decreased to 4.5 micrograms per cubic centimeter in the following hour and a half (table 1). There was no development of color in the samples of aqueous withdrawn three hours after iontophoresis, therefore, the depletion of cyanide from the aqueous is more rapid than that of other compounds (sulfonamide compounds, penicillin).

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11 Emich, F. *Microchemical Laboratory Manual*, New York, J. Wiley & Sons, Inc., 1932, p. 123.

12 Smith, R. G. A Method for the Quantitative Determination of Cyanide in Small Amounts, *J. Am. Chem. Soc.* **51**: 1171 (April 5) 1929.

13 Aldridge, W. N. A New Method for the Estimation of Micro Quantities of Cyanide and Thiocyanate, *Analyst* **69**: 262 (Sept.) 1944.

14 The silver nitrate method was not applicable, since the exposure of samples of normal aqueous to the laboratory air caused the formation of characteristic crystals of silver cyanide. The picric acid method was abandoned because of its unspecificity.

The injurious effect of the neutralized cyanide solution was evidenced not only on the corneal epithelium and the pericorneal and iridal vessels but also on the protein content of the aqueous, which increased considerably. The increase greatly surpassed that observed after iontophoresis with a 0.9 per cent solution of sodium chloride. When a phosphate buffer with a  $p_H$  of 7 or the histamine solution was used, the protein values for the aqueous were sometimes in the same range as, but usually lower than, those for the aqueous of the eyes treated with cyanide. The high protein values for the aqueous were taken to indicate increased permeability of intraocular capillaries.

The cyanide which had entered the posterior chamber could not be measured because of the minute amounts of the fluid in this part of the rabbit's eye. Since the quantities of cyanide in the anterior chamber did not signify whether adequate amounts of the compound had entered the ciliary epithelium, it was advisable to apply the indophenol oxidase

TABLE 1—*Cyanide Content of Aqueous After Iontophoresis with Neutral 0.5 Per Cent Potassium Cyanide*

	Hours After Iontophoresis			
	$\frac{1}{2}$	1	2	3
Cyanide concentration, micrograms/cc	22.50	6.60	3.48	No measurable amount
	44.70	7.20	3.96	No measurable amount
	34.00	16.50-18.80	4.50	No measurable amount
	72.48	14.40	6.10	No measurable amount
Average	43.41	13.50	4.50	No measurable amount

reaction in investigating the inhibition of cyanide and to compare the results with those obtained for control eyes.

*Technic of Experiments on Passage of Penicillin Across the Blood-Aqueous Barrier*—Albino rabbits were killed by withdrawing blood from the heart at various intervals after corneal iontophoresis with neutralized cyanide solution (0.5 per cent) for five minutes at 2 milliamperes. The control eyes received the same iontophoretic treatment with a 0.9 per cent solution of sodium chloride or a phosphate buffer with a  $p_H$  of 7. A 0.1 per cent solution of the histamine dihydrochloride was applied from the anode, as in the preliminary experiments. The enucleated globes were bisected in a frontal plane at the ora serrata.

The lens and vitreous were carefully removed from the anterior segment, and the reagents were dropped on the free inner surface of the ciliary body and on the posterior surface of the iris. The reagents for the oxidase reaction were freshly prepared, according to the modified technic of Winkler and Schultze<sup>15</sup>. This method gave more consistent results in our hands than the method recommended

<sup>15</sup> Mallory, F. B. *Pathological Technique. A Practical Manual for Workers in Pathological Histology, Including Directions for the Performance of Autopsies and for Microphotography*, Philadelphia, W. B. Saunders Company, 1938, p. 185.

by Schmelzer The preparations were examined either with the wide field microscope or in frozen sections with a higher magnification

The same technic was employed on eyes in which the penetration of penicillin across the barrier was studied after the use of the cyanide A dose equivalent to 5,000 units of penicillin per kilogram of body weight was injected intramuscularly one hour after cyanide iontophoresis in one eye and after the control procedure with a 0.9 per cent solution of sodium chloride in the other eye A dose of 8,000 units per kilogram was used when the control eyes were treated with phosphate buffer or with 0.1 per cent histamine dihydrochloride Aqueous was withdrawn thirty minutes after the injection of penicillin One-tenth cubic centimeter of aqueous was used for the assay of penicillin with the filter paper disk method, as described in a later part of this paper, and one-tenth was reserved for the nephelometric determination of the protein content In several instances the penicillin level of the blood was examined at the same time Then the animal was exsanguinated from the heart, and the eyes were dissected for the indophenol oxidase reaction The record of the individual experiments contained, therefore, data on penicillin and protein concentrations in the aqueous and on the results of the test for Warburg's respiratory enzyme in the ciliary epithelium

*Results*—Complete, or almost complete, inhibition in the development of the color reaction in the ciliary epithelium was demonstrated in eyes which had been treated with cyanide thirty minutes to two hours before removal The eyes subjected to the iontophoretic application of a 0.9 per cent solution of sodium chloride or of a 0.1 per cent solution of histamine dihydrochloride showed intensive blue staining of the ciliary processes Densely packed blue granules of various sizes were seen in the ciliary epithelial cells, microscopically presenting the picture which has been described by previous authors<sup>16</sup> The color did not develop as regularly in the eyes in which the phosphate buffer had been used

When the eyes exposed to cyanide were compared with those treated with histamine, the average penicillin content of the former (0.418 unit per cubic centimeter of aqueous) was less than that of the latter (0.502 unit per cubic centimeter of aqueous), despite the inhibition of the respiratory mechanism in the ciliary epithelium and an excessive increase of the protein in the aqueous of the poisoned eyes In this series, 8,000 units of penicillin per kilogram of body weight had been employed The content of penicillin in the aqueous with inhibited respiration of the ciliary epithelium after injection of 5,000 units per kilogram of body weight was 0.23 unit per cubic centimeter, that is twice the amount in the aqueous of eyes treated with sodium chloride (0.11 unit per cubic centimeter), even though the protein content of the former was about six times as great as that of the control eyes (tables 2 and 3) There was a moderate difference between the penicillin levels in the aqueous of eyes exposed to cyanide (0.39 unit per cubic centimeter) and that of the eyes treated with phosphate (0.284 unit

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<sup>16</sup> Seidel<sup>7</sup> Schmelzer<sup>8</sup>

per cubic centimeter), in the former the protein content of the aqueous was about four times that of the latter (table 4) The absolute amounts of penicillin in the aqueous of the series with the use of sodium chloride cannot be compared with those in the two other series because of the difference in the dose of penicillin

TABLE 2—*Penicillin Content of Aqueous and Indophenol Oxidase Reaction of Ciliary Epithelium Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 5,000 Units per Kilogram of Body Weight and Ninety Minutes After Iontophoretic Treatment of One Eye with Potassium Cyanide and of Other Eye with Sodium Chloride*

Units of Penicillin per Cc of Aqueous		Indophenol Oxidase Reaction	
After Iontophoresis With		After Iontophoresis With	
Potassium Cyanide, 0.5%	Sodium Chloride, 0.9%	Potassium Cyanide, 0.5%	Sodium Chloride, 0.9%
0.30	0.10	—	+
0.15	0.10	—	+
0.20	0.15	—	+
0.22	0.12	—	+
0.30	0.10		
Average 0.23	0.11		

TABLE 3—*Protein Content of the Aqueous Ninety Minutes After Iontophoresis with Potassium Cyanide or with Sodium Chloride or After Corneal Bath with Sodium Chloride*

Milligrams of Protein/100 Cc Aqueous		
After Iontophoresis with		After Corneal Bath with 0.9% Sodium Chloride
0.5% Potassium Cyanide	0.9% Sodium Chloride	
See 17 determinations, table 4	116.5	47.2
	94.4	44.2
	164.4	85.2
	106.5	54.0
Average	753.2	54.6

*Comment*—The test for indophenol oxidase, which is based on the oxidation of colorless dimethyl-*p*-phenylenediamine to indophenol blue, demonstrates that Warburg's respiratory enzyme is abundant in the ciliary epithelium and lacking in the stroma. The secretory mechanism in the ciliary processes has been related to the large amount of the enzyme in the ciliary cells or to its unequal distribution between stroma and epithelium. According to Friedenwald and Stiehler, the latter causes a potential difference between these two structures of the

iliary processes which is the source of an ionic current transferring water and cations from the stroma to the epithelium. The difference in potential and the current disappear when the cyanide-sensitive part of the respiratory mechanism in the ciliary epithelium is suppressed. Under this condition, only one component of the blood-aqueous barrier

TABLE 4—*Penicillin and Protein Contents of Aqueous and Indophenol Oxidase Reaction of Ciliary Epithelium Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram of Body Weight and Ninety Minutes After Iontophoresis of One Eye with Potassium or Sodium Cyanide (2 Ma, Five Minutes, from Cathode) or with Histamine Dihydrochloride (1 Ma, Two and One-Half Minutes, from Anode)*

Units of Penicillin per Cc Aqueous After Iontophoresis With		Mg /100 Cc Protein After Iontophoresis With		Indophenol Oxidase Reaction * After Iontophoresis With	
0.5% Potassium Cyanide	Phosphate Buffer	0.5% Potassium Cyanide	Phosphate Buffer	0.5% Potassium Cyanide	Phosphate Buffer
0.18	0.2	308	140		
0.34	0.42	660	135	—	±
0.38	0.30	938	253	—	+
0.83	0.36			—	±
0.52	0.21	926	135	—	+
0.20	0.20			—	—
0.30	0.10	826	130	—	—
Average 0.39	0.28	731.0	158.6		
0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride	0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride	0.5% Sodium Cyanide	0.1% Histamine Dihydrochloride
0.51	0.48	881	348		
0.30	0.51	687	650		
0.41	0.36	759	130		
0.47	0.78	915	565		
0.30	0.78	942	308		
0.43	0.51	450	404		
0.60	0.66	717	180	—	+
0.50	0.50	787	216	—	+
0.20	0.18	1,280	180	—	+
0.72	1.40	445	288	—	+
0.38	0.80	304	308		
0.20	0.50	980	487		
Average 0.418	0.502	762.2	338.7		

\* In this column, — indicates a negative reaction, +, a positive reaction, and ±, a moderately positive reaction.

in the eye, the capillary endothelium should remain unaffected. The permeability of this structure was not left unchanged, however, with the *in vivo* technic used in the present experiments, since the passage of proteins into the anterior chamber must have been caused, at least in part, by the increase in capillary permeability. A comparison of the penicillin levels of the eyes exposed to cyanide with those of the control eyes, which had received iontophoretic treatment with sodium chloride or phosphate buffer, is inconclusive because of the effect of the cyanide

on the intraocular capillaries. The use of histamine dihydrochloride resulted in a rise of the protein level which was comparable in some instances to that observed after cyanide iontophoresis, although it was lower in the majority of experiments. The penicillin levels in 5 experiments were about the same in the eyes treated with histamine and in those treated with cyanide, in 7 globes treated with histamine the penicillin level was higher, despite the relatively lower protein level in 4 of them. As the indophenol oxidase was almost fully inhibited in the eyes treated with cyanide and was not interfered with by the procedures in the eyes subjected to histamine iontophoresis, it is improbable that the epithelial component of the barrier exerts a restraining influence on the passage of the compound from blood to aqueous. The present experimental data point, rather, to an association of the penicillin levels in the aqueous with the permeability of the capillaries of the ciliary processes.

A more definite statement cannot be made without depletion curves for penicillin and protein. In the present experiment such curves could not be obtained because of the evanescent nature of the inhibition of Warburg's enzyme in the ciliary epithelium by cyanide.

Little is known of the action of cyanide on the vascular system and no comprehensive work has been reported on the influence of the compound on capillaries. In the present experiments this influence was studied with the blue tetrazo dye T 1824, which combines and moves with serum albumin and with epinephrine in bleaching threshold doses. The results will be described in detail in another paper. Both tests proved that the capillaries of the limbus were affected by cyanide to a moderate degree. The visible escape of the dye into the tissue of the albinotic iris along the insertion of the ciliary processes on the posterior surface of the iris gave evidence of the great increase in the permeability of the ciliary capillaries due to the metabolic poison. The mechanism of this action of cyanide is still obscure. The inhibition by cyanide of adrenergic responses in certain smooth muscles, as demonstrated by Friedenwald and Buschke,<sup>17</sup> the interference with a theoretic cyanide-sensitive respiratory enzyme system in the capillary wall or a non-specific irritation may be considered as a possible cause of the outpouring of protein.

*Summary*—1 Cyanide was introduced into the anterior chamber by iontophoresis, and it remained there about two hours.

2 The concentrations which reached the ciliary epithelium were adequate to inhibit the cyanide-sensitive part of the respiratory mechanism in this structure for a period of one to two hours.

17 Friedenwald, J. S., and Buschke, W. Effect of Cyanide and Other Metal Binding Substances on the Pharmacological Action of Epinephrine, *Am J Physiol* 140: 367 (Dec.) 1943.

3 Simultaneously there was a steep rise in the protein level of the aqueous, presumably due to a pharmacotoxic action of the cyanide on the capillary endothelium

4 A similar increase in the proteins of the aqueous occurred after histamine iontophoresis without inhibition of the cytochrome oxidase

5 The penicillin content of the aqueous of eyes exposed to cyanide was greater than that of eyes treated with sodium chloride. Experiments with histamine indicated, however, that the increased penetration of penicillin across the blood-aqueous barrier in the eyes subjected to cyanide iontophoresis was probably due to an increase in capillary permeability, and not to an inactivation of Warburg's enzyme in the ciliary epithelium

#### B PENICILLIN LEVELS IN OCULAR AND OTHER BODY FLUIDS AFTER LIGATION OF RENAL VESSELS

Recent studies by Town and Hunt<sup>2c</sup> on the relation of penicillin levels in the blood to those in the aqueous confirmed earlier observations on the inadequate passage of penicillin from blood to aqueous and the effect of paracentesis in obtaining higher concentrations of the drug in the anterior chamber. Massive doses led to an appreciable increase in the penicillin level of the aqueous. The following experiments were conducted to gain more precise knowledge of the connection between the penicillin content of the blood and the levels in the aqueous, vitreous and spinal fluid by preventing renal excretion of penicillin. The depletion of penicillin in the blood in this condition was also considered.

*Technic*—In a series of 8 rabbits, the hilar vessels of each kidney and the branches to the upper pole were securely tied with thick silk after the organs had been exposed by the lumbar approach. Eighteen to twenty-four hours later a solution of sodium penicillin in a dose of 8,000 units per kilogram of body weight was injected intramuscularly. One or three hours after the injection the penicillin content of the aqueous, vitreous, spinal fluid and blood serum was determined with the cup method. In the experiment with the three hour interval between the injection of penicillin and its determination in the body fluids, the blood level was usually examined one, two and three hours after injection.

*Results*—At the selected time intervals, penicillin in the aqueous exceeded by far that in the spinal fluid and vitreous (table 5). In the one hour series the average of 6 observations on the aqueous was 1.25 unit per cubic centimeters, as compared with 0.23 unit per cubic centimeter for the spinal fluid and 0.14 unit per cubic centimeter for the vitreous. The average of 7 determinations of the penicillin level in the blood serum at the one hour interval was 17.4 units per cubic centimeter.

The average of 10 readings on the aqueous at the three hour interval (1.41 unit per cubic centimeter) was slightly higher than that at the one hour interval, whereas the readings on the spinal fluid (average,

0.14 unit per cubic centimeter) and on the vitreous (average, 0.08 unit per cubic centimeter) were lower at this time. The blood level after three hours showed a decrease to about 11.2 units, with great variations in the individual values. The gradients of the depletion curves were similar in 3 instances and considerably less steep in the fourth. In general, high penicillin levels in the blood serum, with a steady decrease during a period of three hours, secured in the aqueous relatively high and well retained penicillin concentrations, which were about 10 per cent of those in the blood serum, whereas only low, steadily decreasing amounts of penicillin were assayed in the spinal fluid and even lower amounts in the vitreous fluid.

TABLE 5—*Penicillin Content of Aqueous, Vitreous, Spinal Fluid and Blood Serum After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram of Body Weight in Rabbits with Ligated Renal Vessels*

Units of Penicillin per Cc							
Hours After Injection	Aqueous		Vitreous		Spinal Fluid	Blood Serum	
	O D	O S	O D	O S			
1	0.34	0.48	0.14	Trace	0.24	8.50	
1	1.18	1.36	0.14	Trace	0.22	17.00	
1	2.12	2.00	0.13	0.22	0.23	20.00	
Average	1.25		0.14		0.23	After (Hours)	
						One	Two
3	2.24	1.58	0.14	0.16	0.27	19.70	
3	1.48	1.04	Trace	Trace	Trace	18.10	11.30
3	0.62	0.86	Trace	Trace	0.12*	17.80	11.50
3	1.76	2.06	Trace	Trace	1.49*	21.80	19.50
3	1.28	1.14	Trace	Trace	Trace	18.60	14.90
Average	1.41		0.08		0.14	17.4	14.1
						11.2	

\* The spinal fluid was mixed with blood, readings were discarded

*Comment*—The experiments on the mechanism of passage of penicillin across the blood-aqueous barrier and the relation between the drug levels of the blood and aqueous were carried out to examine whether the parenteral use of the antibiotic could be applied more effectively against infections of the eye. It was shown in the preceding section that the reason for inadequate amounts of penicillin in the ocular fluids after its systemic use probably does not lie in a selective retention of the substance by the blood-aqueous barrier.

The experimental data on renal blockage point to the importance of two factors as causes of the unsatisfactory drug levels in the eye. They are the steep decline of the penicillin content of the blood due to renal clearance within one hour after injection and the comparatively low concentration of about 0.1 unit per cubic centimeter in the blood.



during continuous treatment. When excretion was prevented and a high peak blood level was maintained over a prolonged period, the penicillin level of the aqueous (1.41 unit per cubic centimeter) amounted to about 10 per cent of the penicillin content of the serum. It is evident, therefore, that serum levels below 0.5 unit per cubic centimeter cannot provide aqueous concentrations which are assayable with the cup method.

In contrast with the slight increase of the penicillin values for the aqueous during the observation of three hours was the decrease in the drug level of the vitreous in the same period. No explanation can be offered for this difference, as vitreous fluid did not inactivate the antibiotic *in vitro*. The decrease in the penicillin concentration of the blood of these experimental animals within three hours may be due in part to the diffusion of the compound into the tissue fluids. Small amounts of penicillin are secreted in the bile and saliva of nephrectomized animals, according to Cutting and co-workers<sup>18</sup>. These authors also suggested the possibility of some destruction of the compounds by reticuloendothelial cells.

Liebman and Newman,<sup>19</sup> in their studies on the distribution of sulfonamide compounds between blood and aqueous, reported that the average aqueous contents, expressed in percentages of the serum level, were 13.4 for sulfapyridine and 17.4 for sulfathiazole, these values, therefore, were in the same range as the corresponding figures for the penicillin experiments. Sulfadiazine penetrated three to four times as well as the two other sulfonamide compounds. A comparison of the rates of depletion of sulfonamide compounds and penicillin in the eye shows that in a four hour period the sulfadiazine content of the aqueous decreases to one-fourth, and the penicillin content to less than one-sixth, the original concentration. This difference between the speed of absorption of the two antibiotics in the aqueous is a second factor which may account for the comparatively moderate amounts of penicillin in the aqueous several hours after administration.

In general medicine the renal clearance of penicillin was depressed by the simultaneous administration of para-aminohippuric acid, which obviously competed with penicillin for the same renal excretory mechanism.<sup>20</sup> Iodopyracet injection U.S.P. ("diodrast")<sup>21</sup> and benzoic acid<sup>21a</sup>

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18 Cutting, W. C., Luduene, E. P., Fiese, M., Elliott, H. W., and Field, J., II. Distribution and Fate of Penicillin in the Body, *J. Pharmacol. & Exper. Therap.* **85**: 36 (Sept.) 1945.

19 Liebman, S. D., and Newman, E. H. Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, *Arch. Ophth.* **26**: 472 (Sept.) 1941.

20 Beyer, K. H., Woodward, R., Peters, L., Verwey, W. F., and Mattis, P. A. Prolongation of Penicillin Retention in the Body by Means of Para-

were also used for this purpose, with favorable results. Delayed absorption of penicillin was obtained with potassium sulfate and by the administration of penicillin in beeswax and peanut oil<sup>22</sup>. For the same purpose, ossein gelatin was used as a vehicle and the penicillin combined with a vasoconstrictor drug<sup>23</sup>.

In the present experiments, the relation between high penicillin levels in the blood and satisfactory concentrations in the aqueous was clearly demonstrated. Town and Hunt showed that the prolongation of low or medium drug levels in the blood did not influence the blood-aqueous ratio of the compound. It can be assumed, therefore, that procedures which reduce the renal excretion of penicillin after a massive dose, rather than those which delay absorption from the depot in the muscles, should be considered in the treatment of severe ocular infections.

*Summary*—1. When the hilar vessels of the kidney and the branches to the upper pole were ligated, the parenteral injection of penicillin was followed by high blood levels, which declined slowly within three hours to about one-third the amount measured after one hour.

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21. Rammelkamp, C. H., and Bradley, S. E. Excretion of Penicillin in Man, *Proc. Soc. Exper. Biol. & Med.* **53** 30 (May) 1943.

21a. Bohls, S. W., and Cook, E. B. M. Use of Aluminum-Penicillin Mixtures in Maintenance of Blood Levels of Penicillin. II. Combination of Delayed Absorption by Use of Aluminum-Penicillin and Renal Blockage with Benzoic Acid, *Texas State J. Med.* **41** 342 (Nov) 1945.

22. Romansky, M. J., and Rittman, G. E. A Method of Prolonging the Action of Penicillin, *Science* **100** 196 (Sept) 1944. Penicillin. I. Prolonged Action in Beeswax-Peanut Oil Mixture, II. Single Injection Treatment of Gonorrhea, *Bull. U. S. Army M. Dept.*, October 1944, no. 81, p. 43. Romansky, M. J., Murphy, R. J., and Rittman, G. E. Single Injection Treatment of Gonorrhea with Penicillin in Beeswax-Peanut Oil. Results in One Hundred and Seventy-Five Cases, *J. A. M. A.* **128** 404 (June 9) 1945. Romansky, M. J., and Rittman, G. E. Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, *New England J. Med.* **233** 577 (Nov 15) 1945. Nichols, D. R., and Hanuz, E. A. Prolonged Action of Penicillin in Mixtures of Beeswax and Peanut Oil, *Proc. Staff Meet., Mayo Clin.* **20** 403 (Oct) 1945. Kirby, W. M. M., Leifer, W., Martin, S. P., Rammelkamp, C. H., and Kinsman, J. M. Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil, *J. A. M. A.* **129** 940 (Dec 1) 1945.

23. Parkins, W., Wiley, M., Chandy, J., and Zintel, H. A. Maintenance of the Blood Level of Penicillin After Intramuscular Injection, *Science* **101** 203 (Feb 23) 1945.

2 The aqueous contained an average of 1.4 units per cubic centimeter at the three hour period. This was about one-tenth the penicillin concentration in the blood.

3 The level of penicillin in the vitreous and spinal fluid remained low despite its increase in the blood.

#### C PASSAGE OF PENICILLIN FROM BLOOD INTO AQUEOUS AND VITREOUS IN OCULAR INFLAMMATION

Earlier studies, as well as those in the preceding experiments, suggested that the penetration into the aqueous was enhanced by dilatation of the capillaries. On this basis could be explained the effect of paracentesis,<sup>2</sup> intraocular injections of histamine,<sup>1d</sup> instillations of peroxide<sup>3b</sup> and the procedures described in the first part of this study. These experiments did not indicate, however, the extent to which an intraocular inflammation influenced the passage of penicillin across the blood-aqueous barrier. In the present study, a self-limiting inflammation of varying severity was produced by injecting staphylococcus toxin (staphylotoxin) into the vitreous. The clinical stage of the inflammatory process and the penicillin levels in the intraocular fluids were compared.

*Technic*—In general, the staphylococcus toxin was prepared according to the technic of Leonard and Holm.<sup>24</sup> A strain of *Staphylococcus aureus* BD, supplied by the department of bacteriology, Columbia University College of Physicians and Surgeons, was grown in Kolle bottles on the semisynthetic, infusion-free medium recommended by Leonard and Holm. The inoculated bottles were placed in an atmosphere of 80 per cent carbon dioxide and 20 per cent oxygen, and the cultures were harvested after incubation for forty-eight hours. The content of the bottles was first filtered through filter paper and the filtrate centrifuged. The supernatant was siphoned off, adjusted to a  $pH$  of 6.8 and filtered through a diatomaceous filter of medium porosity. The toxin was tested for sterility, and its hemolytic titer and dermonecrotic activity were determined according to general rules.

Tentative experiments showed the effect of intravitreal injections of the undiluted toxin. In the subsequent series, 0.05 to 0.1 cc was injected into the vitreous of one eye of each rabbit in a group of 10 rabbits. The other eye was used as a control. The development and progress, as well as the regressive changes, of the inflammation were studied with the slit lamp and with the ophthalmoscope. At various stages of the inflammation, aqueous and vitreous fluid were examined for penicillin activity with the cup method half an hour after the intramuscular injection of sodium penicillin, equivalent to 8,000 units per kilogram of body weight. When the vitreous was examined, its appearance after withdrawal from the eye was recorded. Samples of blood for determination of penicillin were taken from the heart or ear shortly before withdrawal of the ocular fluids.

*Results*—The staphylococcus toxin had a high titer of 4,000 minimum hemolytic doses. The dermonecrotic action was pronounced, but the minimal dermonecrotic dose was not determined. The eyes were

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24 Leonard, G. F., and Holm, A. A Method for Production of *Staphylococcus* Toxin and Toxoid, *J. Immunol.* **29**: 209 (Sept.) 1935.

divided into two groups according to the stage of inflammation. In the eyes of the first group, signs of severe acute endophthalmitis were present, such as ciliary injection, exudate or dense flare and cellular deposits in the anterior chamber, extreme swelling and hyperemia of the iris and diffuse cloudiness in the vitreous. Details of the fundus could not be seen or were barely visible. The eyes of the second group showed less injection of the globes, a small number of cells and moderate flare in the aqueous and slight swelling of the iris. Details of the fundus were somewhat blurred by faint cloudiness in the vitreous.

Table 6 shows that the intensity of the acute inflammation had a definite bearing on the amount of penicillin in the aqueous, as it con-

TABLE 6—*Penicillin Content of Aqueous and Vitreous Thirty Minutes After Intramuscular Injection of Sodium Penicillin Equivalent to 8,000 Units per Kilogram in Rabbits with Endophthalmitis Induced with Staphylococcus Torii*

Type of Inflammation	Days After Injection of Staphylococcus Toxin	Units of Penicillin per Cubic Centimeter				Blood Serum
		Aqueous, in Inflamed Eyes	Vitreous, in Inflamed Eyes	Aqueous, in Control Eyes	Vitreous, in Control Eyes	
Severe	5	0.42		0.13		2.33
Severe	7	0.85	0.12	0.16	0.10	2.06
Severe	7	1.33	0.11		0.08	4.00
Severe	3	1.29	0.16	0.40	0.09	
Severe	5	1.08	0.14	0.16	0.10	
Severe	5	1.17		0.17		2.00
Average		0.98	0.13			
Mild	6	0.39		0.08		
Mild	12	0.12		0.11		3.70
Mild	11	0.39		0.12		2.90
Mild	10	0.46		0.12		4.00
Average		0.34		0.15	0.09	3.00

tained an average of almost 1 unit per cubic centimeter in the severely inflamed eyes. When the signs of the endophthalmitis had regressed greatly, the penicillin content of 0.34 unit per cubic centimeter was more than twice that of the normal eyes, with 0.15 unit per cubic centimeter. In all instances the penicillin level was higher in the aqueous of the inflamed eyes than in the control eyes.

Only slightly more penicillin was determined in the vitreous of the acutely diseased eyes than in that of the normal eyes. This observation was unexpected in the case of globes with newly formed vessels in membranes extending from the detached retina into the vitreous. The penicillin levels in the samples of blood which were withdrawn at about the same time as the intraocular fluids were not clearly related to the concentrations in the aqueous.

*Comment*—Clinical reports on penicillin therapy of intraocular infections deal, in general, with cases in which the etiologic agent was unknown. The failure of systemic penicillin treatment, obviously, cannot be evaluated in these instances, as the presence of organisms susceptible to penicillin cannot be demonstrated.

Favorable observations on systemic penicillin therapy have not been recorded in cases of infections of the human vitreous, nor has this type of treatment been tested in a sufficient number of patients with acute ectogenous infections of the anterior segment. In experimental studies unsatisfactory results with intramuscular injection of penicillin were reported by Leopold<sup>14</sup> when the vitreous was inoculated with cultures of sensitive organisms. Infections which Town and co-workers<sup>25</sup> produced in the rabbit's anterior chamber with a highly susceptible hemolytic streptococcus responded well so far as the corneal infiltration was concerned. On the other hand, corneal ulcers produced by a gram-negative, penicillin-sensitive rod were treated by Leopold and co-workers<sup>26</sup> more effectively by local means than by intramuscular administration of penicillin, and Miller and co-workers<sup>27</sup> noticed the failure of parenteral treatment of gonococcal infections of the anterior segment with penicillin in large doses. These inconsistent results may be explained by differences in the administered dose, in the character of the inflammation and in the susceptibility of the organisms.

Massive doses increased the level in experimental animals, but much higher values (about 1 unit per cubic centimeter) were determined for acutely and severely inflamed eyes in the current experiments. This amount was more than six times the average value for penicillin obtained in the aqueous of the normal eyes, in moderately inflamed eyes the penicillin level was about twice that in the controls. The dose in these experiments was in the range recommended for certain cases of endocarditis, meningitis and cerebrospinal syphilis.

The results of the present investigation indicate that infective foci in the vitreous will not be decisively influenced by systemic therapy, but high peak blood levels may be useful in supporting energetic local treatment, or even in substituting for it in the case of acute ectogenous infections of the anterior segment. The observations of Town and co-workers point to the value of this therapeutic approach, although

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25 Town, A. E., Frisbee, F. C., and Wisda, J. G. Penicillin Control of Ocular Infection, *Am J Ophth* **29** 341 (March) 1946.

26 Leopold, I. H., Holmes, L. F., and La Motte, W. O., Jr. Local Versus Systemic Penicillin Therapy of Rabbit Corneal Ulcer Produced by Gram-Negative Rod, *Arch Ophth* **32** 193 (Sept.) 1944.

27 Miller, C. P., Bohnhoff, M., and Moeller, V. Experimental Gonococcal Infection of the Rabbit's Eye. III. Treatment with Prophylactic and Therapeutic Agents, *J Infect Dis* **77** 216 (Nov-Dec) 1945.

similar infections with the hemolytic streptococcus responded well to parenteral treatment with sulfanilamide. In view of the ineffectiveness of parenteral use of penicillin in cases of experimental gonococcic endophthalmitis of the anterior segment, however, no predictions can be made, especially with regard to the prognosis of infections with other penicillin-sensitive organisms.

Foci which are not exposed to the aqueous and which occur in deeper parts of vascularized tissue are accessible to the therapeutic agent circulating in the blood. On the basis of experimental evidence with massive doses of penicillin in inflamed eyes, better results may be anticipated in such conditions by increasing the usual clinical dose to that recommended for the aforementioned diseases. Local application of vasodilator substances may be a valuable adjuvant. The trauma of paracentesis in infected eyes of rabbits was found to be of definite disadvantage in the experiments of Town and co-workers. Their results suggest great caution in employment of this procedure.

*Summary*—1 Acute, self-limiting endophthalmitis was produced by injecting staphylococcus toxin into the vitreous of rabbits.

2 The amount of penicillin determined in the aqueous after parenteral injection of massive doses of penicillin depended on the stage of the inflammatory process. With severe acute inflammations the aqueous level reached an average of 1 unit per cubic centimeter, it exceeded moderately that for normal eyes when the inflammation was in the regressive stage.

3 The penicillin level of the vitreous always remained very low under the experimental conditions studied.

## II SURFACE APPLICATIONS OF PENICILLIN IN OPHTHALMOLOGY

### A SOLUTIONS AND OINTMENTS

The common clinical procedures were utilized for topical ocular penicillin therapy. Depending on the site of the infection, preference was given to instillations of aqueous solutions or ointments, to the use of cotton packs or penicillin crystals, to corneal baths or iontophoretic introduction and to injection of solutions of penicillin under the conjunctiva or into the anterior chamber, lens or vitreous. In the treatment of certain surface infections with drops or ointments, the desirable concentration of penicillin in the vehicle and the frequency of use were matters of controversy. Concentrations from 50 to 20,000 units per cubic centimeter or per gram were recommended. Brown,<sup>28</sup> in his study

28 Brown, C. A. Penicillin in Ophthalmology. Bacteriological, Experimental and Clinical Evidence of Its Value, Including a Personal Series of One Hundred and Twenty-Five Clinical Cases, *Brit. J. Ophth.* **30** 146 (March) 1946.

of long-observed patients with conjunctivitis and blepharitis, proved that ointments containing 1,000 units per gram of base prevented relapses more readily than weaker preparations. More clinical evidence is necessary to show the advantage of high dosage in the treatment of corneal infections claimed by several authors (Juler and Johnson<sup>29</sup>) and questioned by others (Rycroft<sup>1e</sup>). Experience with penicillin therapy of well observed uncommon infections of the lids and conjunctiva is also too limited to permit general conclusions. In view of the debatable reliability of standard lesions in these parts of the eye of laboratory animals, little information can be expected from experimental studies, but the usefulness of local procedures is strongly suggested by the results of Leopold<sup>2e</sup> and Robson and Scott<sup>30</sup>.

Experiments with various ointment bases and with various penicillin salts have been carried out<sup>31</sup> and results reported in regard to stability and penetration of the drug<sup>32</sup>. Data on the absorption from aqueous solutions are also available<sup>33</sup>. The question of an adequate frequency of instillations still meets with considerable uncertainty, as it depends on the morbid anatomy of the lesion and the susceptibility of the organisms to penicillin. Besides, little is known about persistence of penicillin action in the conjunctival sac after instillation. Milner<sup>34</sup> modified the Fleming slide cell method for estimating the penicillin content of conjunctival secretion at different intervals after instillation of penicillin drops or ointments. Reliable results could not be achieved in this laboratory with a similar technic. The quantities of the samples of tears could not be measured accurately with micropipets despite the use of lacrimators. The samples were frequently contaminated with penicillin-resistant organisms, which render the test valueless. It was soon obvious that the filter paper disk modification of the cup method,

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29. Jules, F., and Johnson, G. T. Use of Crystalline Penicillin in Corneal and Intraocular Infections, *Brit J Ophth* **30** 204 (April) 1946.

30. Robson, J. M., and Scott, G. I. Production and Treatment of Experimental Pneumococcal Hypopyon Ulcers in the Rabbit, *Brit J Exper Path* **24** 50 (April) 1943, Local Chemotherapy in Experimental Lesions of the Eye Produced by *Staphylococcus Aureus*, *Lancet* **1** 100 (Jan 23) 1943, Experimental Streptococcal Lesions of the Rabbit's Eye and Their Treatment, *Brit J Exper Path* **25** 81 (June) 1944.

31. Keyes, J. E. L. Penicillin in Ophthalmology, *J A M A* **126** 610 (Nov 4) 1944. Minton, J. Penicillin in Treatment of Common External Eye Infections, *Brit M J* **2** 324 (Sept 7) 1946. Merory, P. H., McAnally, D., and Picard, C. W. Penicillin for External Eye Infections, *ibid* **2** 513 (Oct 5) 1946.

32. von Sallmann, L., Grosso, A. E., and Marsh, M. G. Ophthalmic Penicillin Ointments, *Arch Ophth* **36** 284 (Sept) 1946.

33. von Sallmann and Meyer<sup>1a</sup>. Bellows<sup>1c</sup>. Leopold<sup>1d</sup>.

34. Milner, J. G. Penicillin in Ophthalmology, *Brit M J* **2** 175 (Aug 5) 1944.

described by Vincent and Vincent<sup>35</sup> and recommended also by De Beei and Sherwood,<sup>36</sup> was better suited to our purpose

*Technic*—Normal eyes of volunteers were used for the determination of the penicillin content of the tear fluid three, six and eight hours after instillation of penicillin drops in the right eye and of ointment containing the drug in the left eye. Eighty-four samples of tears were tested, including 8 control samples from untreated human eyes. Two drops of a solution of sodium penicillin containing 1,000 units per cubic centimeter was instilled into the lower cul-de-sac. The ointment, also containing 1,000 units of penicillin per gram, was pressed out of a collapsible tube on the surface of the lower fornix in the form of a double ribbon the length of the palpebral fissure. At the selected intervals of time, the lid borders of the eyes, which had received the penicillin drops were cleaned with an 0.9 per cent solution of sodium chloride. Remnants of the ointment were removed from the surface of the lids by sponging with 80 per cent alcohol and with a solution of sodium chloride. Freshly cut onions were used as lacrimators. The first tears secreted were collected by two examiners at the same time from the two eyes by touching the tear fluid at the everted lower conjunctival fornix with the lower edge of a sterilized standard filter paper disk until its upper edge appeared dampened. Contact was avoided between the lid border and the filter paper, which was held in a sterile forceps. The disks were then placed equally distant from each other on seeded agar plates. Disks dampened in standard solutions of penicillin in a similar way were added to each plate so that triplicates of each dilution could be read. The zones of inhibition were evaluated as usual. Traces below 0.1 unit per cubic centimeter were judged from the density of the colonies in the area covered by the disk as seen under the wide field microscope.

*Results*—It is evident from table 7 that the readings varied considerably within the same group of experiments on the same subject and among the individual subjects. In all eyes treated with an aqueous solution there was with time a continuous decrease in the assayable amount of penicillin. With 1 exception, in which slightly more penicillin was determined after three hours than after one hour, a similar decrease was observed in the eyes of 2 subjects treated with ointment. Several factors may account for the wide irregularities in the readings, but the main factor is undoubtedly the variation in the amount of tearing produced by the lacrimator and the consequent dilution of the penicillin in the sample. In general, the difference between the results with the two types of procedure was negligible. In the three and in the six hour series of experiment 2, the readings for the eyes treated with drops ran consistently higher than those obtained on the eyes with ointment. It is probable that in this experiment the ointment caused more irritation and loss of penicillin by reflex tearing. With 1 excep-

35 Vincent, J. G., and Vincent, H. W. Filter Paper Disc Modification of the Oxford Cup Penicillin Determination, *Proc Soc Exper Biol & Med* **55** 162 (March) 1944

36 De Beer, E. J., and Sherwood, M. B. The Paper-Disc Agar-Plate Method for the Assay of Antibiotic Substances, *J Bact* **50** 459 (Oct) 1945



tion, positive results were obtained with all samples of tears collected after six hours. The majority of tests made after eight hours also showed penicillin activity. Tears from untreated (control) eyes caused sparser growth beneath the filter paper disks, but the number of colonies exceeded those which were present after removal of the disks dampened in a phosphate buffer solution of  $p_H$  6.8.

*Comment*—The results of these experiments can be compared only in part with those of Milner, since he used solutions containing 500 units per cubic centimeter and an ointment with 100 units per gram and did not determine quantitatively the penicillin in the samples of conjunctival

TABLE 7—*Penicillin Content of Tear Fluid at Various Intervals After One Instillation of Aqueous Solution or Ointment Containing Sodium Penicillin Equivalent to 1,000 Units per Cubic Centimeter or per Gram*

Hours After Instillation	Units of Penicillin per Cc Tear Fluid						Untreated (Control) Eyes	
	1		2		3		O D Drops	O S Ointment
	O D Drops	O S Ointment	O D Drops	O S Ointment	O D Drops	O S Ointment		
3	0.07	0.53	1.71	0.14	0.11	0.16	0.00	0.00
	0.15	2.00	0.45	0.17	0.19	0.37	0.00	0.00
	0.19	0.36	0.47	0.285	0.41	0.10	0.00	0.00
	0.16	0.07	1.40	0.07	0.00	0.10	0.00	0.00
Average	0.14	0.54	0.95	0.23	0.18	0.18	0.00	0.00
6	0.09	0.11	0.46	0.09	0.11	0.11		
	0.19	0.14	0.15	0.78	0.12	0.27		
	0.08	0.23	1.42	0.325	0.09	0.00		
	0.59	0.14	1.38	0.16	0.08	0.08		
Average	0.23	0.15	0.82	0.29	0.10	0.11		
8	0.14	0.80	0.18	0.41	0.00	0.10		
	0.00	0.10	0.54	0.78	0.00	0.11		
	0.07	0.00	0.27	0.08	0.09	0.07		
	0.07	0.00	0.55	0.09	0.11	0.07		
Average	0.07	0.10	0.32	0.33	0.05	0.09		

fluid. In contrast with Milner's results, there was no indication that penicillin remained longer in the conjunctiva after the use of ointment. In the present series, penicillin activity was observed in four fifths of the samples as long as eight hours after treatment. This finding suggests that instillations of penicillin can be sufficiently effective when given at intervals longer than are usually recommended, provided that the organisms are of average sensitivity and that the inflammation is not accompanied with epiphora. It is advisable to keep in mind the prolonged action of penicillin in the conjunctiva after one instillation when eyes are to be examined bacteriologically.

*Summary*—1 The concentration of penicillin in tears was conveniently estimated with the filter paper disk method of Vincent and Vincent.

2 Tears of normal human eyes displayed penicillin activity in almost all instances six hours after instillation of a solution or an ointment containing 1,000 units per cubic centimeter or per gram. Eight hours after the treatment four fifths of the samples still possessed assayable amounts of penicillin.

3 The quantities of penicillin in the tears were about the same, and penicillin activity was observed for the same length of time regardless of whether ointment or solutions had been employed.

#### B IONTOPHORETIC INTRODUCTION OF PENICILLIN

The value of cotton packs for stepping up the concentration in the anterior segment of the eye was discussed in a previous paper.<sup>37</sup> Since there was no disagreement on this form of therapy, no further studies were carried out in the present work. Opinions differ on the usefulness of introducing penicillin by iontophoresis. It was desirable, therefore, to investigate some factors operative in the penetration of penicillin into the eye under an impressed potential, the inactivation of penicillin due to changes of the  $p_H$  at the cathode, and the value of two types of clinical iontophoresis.

The principal objections to the rationale of penicillin iontophoresis have been voiced by Hamilton-Paterson.<sup>38</sup> On the basis of experiments with solutions of commercial penicillin, 25 and 50 units per cubic centimeter, the author arrived at the conclusion that penicillin is either a very poor conductor or a nonconductor. Without sufficient consideration to the extensive experimental data on this subject, Hamilton-Paterson expressed doubt whether a therapeutic concentration could ever be obtained in the tissue by means of iontophoresis. He commented further on the strong possibility that the penicillin would be destroyed by the products of electrolysis of other electrolytes present and assumed that any attempts to introduce penicillin into the body by ionization were doomed to failure. It may be sufficient to counter with the results of a few experiments, which are easily reproducible.

1 *Conductivity of Sodium Penicillin*—Ten milligrams of crystalline sodium penicillin G of a potency of 1,570 units per milligram<sup>39</sup> was dissolved in 3 cc of conduction water (333 mg per hundred cubic centimeters). The concentration of this solution approximates that

37 von Sallmann, L. Penetration of Penicillin into the Eye. Further Studies, Arch Ophth **34** 195 (Sept) 1945.

38 Hamilton-Paterson, J. L. The "Ionization" of Penicillin, Brit M J **1** 680 (May 4) 1946.

39 This penicillin was provided by Dr. O. Wintersteiner, of Squibb Institute for Medical Research. Although the preparation was analytically pure, the absence of small amounts of other penicillins (X, K, and F) was not guaranteed. The content of such impurities was not likely to exceed 10 per cent.

used in ocular iontophoresis Dr Dan H Moore, director of the electrophoretic laboratory, department of anatomy, Columbia University College of Physicians and Surgeons, determined the conductivity of the solution, with the following results

$$\frac{\begin{array}{l} \text{KH}_2\text{O} \\ \text{K penicillin} \end{array}}{\text{KH}_2\text{O}} = \frac{\begin{array}{l} 1.09 \times 10^{-6} \text{ mho} \\ 290.00 \times 10^{-6} \text{ mho} \end{array}}{1.09 \times 10^{-6}} = 266$$

That is, the conductivity of the water was increased 266 times by adding crystalline sodium penicillin G in a concentration of 333 mg per hundred cubic centimeters

## 2 Influence of Change in $p_H$ at Cathode on Activity of Penicillin —

The destruction of penicillin by the shift of the  $p_H$  to the alkaline side when the cathode was immersed in the penicillin solution was discussed in a report from this laboratory in 1945<sup>40</sup> The inactivation of penicillin by the increased  $p_H$  of the milieu around the negative terminal depends on the depth of immersion of the terminal, the density of the current, the duration of the treatment and the amount of penicillin solution in the applicator tube In the previous study on the relation between the capacity of the applicator tube and the inactivation of the penicillin, the technic was not described, and a more detailed report seemed advisable

**Technic** Three types of applicators were selected for the tests a Birkhäuser electrode used with 2 to 3 cc of a solution of penicillin, a punctuated Stocker electrode which contained a cotton sponge saturated with 1 to 1.5 cc of penicillin solution, and, finally, a thin cylindric tube which held 0.5 to 1.0 cc of the electrolyte The application time of five minutes, a current of 2 milliamperes and the concentration of penicillin (1,000 units per cubic centimeter) were constant In the experiments with the Birkhäuser electrode the hydrogen ion concentration of the penicillin solution was estimated with indicator paper at the beginning of the procedure and after two and one-half and after five minutes In this electrode the depth of immersion of the terminal was approximately 1.5 cm

**Results** As table 8 shows, the loss of antibiotic activity of the penicillin solution amounted to 60 per cent or more when very small quantities of the electrolyte were employed It was previously pointed out that the destruction of the penicillin would be almost complete in the iontophoretic treatment of the root canals of the teeth because of the minute amount of solutions used in this method The penicillin solution was prepared with a 0.9 per cent solution of sodium chloride This solvent was slightly acid ( $p_H$  about 6), having been exposed for some time to the laboratory air In corneal iontophoresis with the Birkhäuser or the van Heuven electrode, the  $p_H$  of the fluid almost reached the neutral point in two and one-half minutes and shifted in the

40 von Sallmann, L The Role of Iontophoresis with Antibiotics in Ocular Therapy, New York J Dent 15 261 (Oct) 1945

following two and one-half minutes to a  $p_H$  between 8.6 and 9.4. The testing of samples from the solution in the applicator tube after five minutes of electrolysis indicated a loss of about 13 per cent of penicillin activity, that is, a negligible decrease of potency. It can be assumed that the inactivation of the compound will be in the same range as that with other electrodes of similar capacity.

3 *Factors Acting on Passage of Penicillin Through Cornea During Iontophoresis*—It was demonstrated in many experiments that high concentrations of penicillin could be procured in the anterior segment of the rabbit and human eye by corneal iontophoresis. The penetration was about four to twenty times as great as with the corneal bath. It was also shown that the concentration of the penicillin solution, the milliamperage of the current, the length of treatment and the use of the anesthetic have a bearing on the amount of the compound introduced into the anterior chamber. It is not known whether there is an ion

TABLE 8—*Percentual Loss in Activity of a Solution of Sodium Penicillin Equivalent to 1,000 Units per Cubic Centimeter After Iontophoresis for Five Minutes from the Cathode at 2 Ma. with Three Types of Applicator Tubes*

Type of Tube	Fluid Content of Tube, Cc	Loss of Activity, per Cent
Birkhauser	2.3	13
Stocker	1.15	58
Thin, conic	0.51	61

transfer (iontophoresis) or a transportation of the fluid with the undissociated salt (electro-osmosis), or whether the permeability of the cornea is increased by the flow of the electric current or a change in the  $p_H$  of the milieu. In the present experimental study, several factors are considered which may account for the relatively great amounts of the electrolyte in the anterior chamber after corneal iontophoresis. They are (a) the effect of the flow of the electric current, (b) the changes in the hydrogen ion concentration in the electrolyte solvent, (c) the polarity of the terminal and (d) the tonicity of the penicillin solution.

#### (a) Effect of Flow of Electric Current from Cathode

**Technic** In 10 rabbits the right eye was treated iontophoretically with 0.9 per cent solution of sodium chloride for five minutes at 2 milliamperes from the cathode. The other eye received a corneal bath with this solution for the same length of time. After these procedures, both eyes were exposed to a corneal bath with a solution of sodium penicillin containing 2,000 units of penicillin per cubic centimeter for five minutes. The penicillin content of the aqueous was determined one hour later. The results were compared with those obtained by the iontophoretic introduction of penicillin in 0.9 per cent solution of sodium chloride containing 2,000 units of penicillin per cubic centimeter at 2 milliamperes for five minutes.

The changes in the  $p_H$  of the solutions due to the passage of the electric current were estimated with indicator paper

**Results** One hour after the sodium chloride bath and penicillin bath, the average penicillin concentration of the aqueous of the left eye was 0.39 unit per cubic centimeter, whereas the average penicillin content of the aqueous of the right eye, which had been exposed to iontophoresis with the solution of sodium chloride, followed by a penicillin bath, was about six times as great, with an average of 2.24 units per cubic centimeter (table 9). However, an average of 5.3 units per cubic centimeter was estimated in the aqueous one hour after a solution of

TABLE 9—*Penicillin Content of Aqueous One Hour After Five Minute Corneal Bath with Solution Containing Sodium Penicillin Equivalent to 2,000 Units per Cubic Centimeter Which Followed Iontophoresis with Sodium Chloride of One Eye and Corneal Bath with Sodium Chloride of Other Eye*

Corneal Bath with Sodium Penicillin (2,000 Units per Cc) for Five Minutes Following		
Iontophoresis with 0.9% Sodium Chloride at 2 Ma for Five Minutes	Corneal Bath with 0.9% Sodium Chloride for Five Minutes	Iontophoresis with Sodium Penicillin (2,000 Units per Cc) at 2 Ma for Five Minutes
Units Penicillin per Cc Aqueous		
1.6	0.4	6.4
1.6	0.4	6.4
1.6	0.8	3.2
1.6	0.2	6.4
3.2	0.1	3.2
0.8	0.4	6.4
1.6	0.2	
0.8	0.4	
6.4	0.4	
3.4	0.2	
Average 2.24	0.39	5.3

penicillin of the same strength was applied at 2 milliamperes for five minutes. The  $p_H$  of the solutions of sodium chloride and of sodium penicillin increased from 6.2 to a maximum of 9.4 during the passage of the current.

#### (b) Effect of Changes in Hydrogen Ion Concentration of the Bathing Fluid

**Technic** In a series of 6 rabbits the right cornea was subjected to a bath for two and one-half minutes of a 0.9 per cent solution of sodium chloride which had been adjusted with sodium hydroxide to a  $p_H$  of 9.4. This was followed by a corneal bath with a solution of sodium penicillin containing 5,000 units per cubic centimeter for five minutes; the same procedure was adopted for the left eye except that the solution of sodium chloride had a  $p_H$  of 6. Determination of penicillin in the aqueous was again carried out one hour after treatment.

**Results** These experiments were undertaken in view of the possibility of a change in the permeability of the corneal epithelium due to brief exposure to a milieu of a  $p_H$  between 8.6 and 9.4. The  $p_H$  of the sodium chloride bath which preceded the penicillin bath had no significant effect on the permeability of the cornea for the antibiotic, as demonstrated by the penicillin content of the aqueous, it averaged 1.7 units per cubic centimeter for the right eyes and 1.6 units per cc for the left eyes (table 10).

(c) Effect of Polarity of Terminal

**Technic** In a series of 10 rabbits, the right eye received cathode iontophoresis with a solution of sodium penicillin, equivalent to 5,000 units per cubic centimeter, for two minutes, the left eye was similarly treated with anode iontophoresis. In 10 additional eyes, a corneal bath was applied for the same length of time with a

TABLE 10—*Penicillin Content of Aqueous One Hour After Five Minute Corneal Bath with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter Which Followed Corneal Bath with an Alkalinized Solution of Sodium Chloride ( $p_H$  9.4) on One Eye and Corneal Bath with Untreated Solution of Sodium Chloride ( $p_H$  6) on Other Eye*

Units of Penicillin per Cubic Centimeter Aqueous After a Corneal Bath of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter for Five Minutes Following a Corneal Bath of Two and One Half Minutes with		
0.9% Sodium Chloride at $p_H$ 9.4		0.9% Sodium Chloride at $p_H$ 6
Units Penicillin per Cc Aqueous		
1.6		1.6
3.2		1.6
0.8		1.6
1.6		1.6
1.6		1.6
1.6		1.6
Average 1.7		1.6

solution of penicillin of the same strength. The concentration of penicillin in the aqueous was determined one hour after the various procedures.

**Results** Iontophoreses with penicillin from the cathode was compared with that from the anode to clarify the nature of the transfer. When the length of the treatment was reduced to two minutes, the effect of the changes in  $p_H$  on penicillin was practically avoided. There was about four times as much penicillin in the aqueous after iontophoresis from the cathode (2.08 units per cubic centimeter) as after treatment from the anode (0.56 unit per cubic centimeter) (table 11). Only a small difference was evident between the amount of penicillin in the anterior chamber of eyes treated from the anode and that for the control eyes, which had received a simple bath with a penicillin solution of the same strength for the same length of time (0.38 unit per cubic centimeter).

## (d) Effect of Tonicity of Penicillin Solution

Technic Solutions of sodium penicillin were made up accurately in a concentration of 2,000 units of penicillin per cubic centimeter in distilled water and in 0.9 per cent solution of sodium chloride. The right eye of 6 rabbits was treated iontophoretically at 2 milliamperes for five minutes with the strongly hypotonic solution, and the left eye, with the nearly isotonic solution. One hour after the procedure the aqueous was withdrawn for the determination of penicillin. In 8 rabbits corneal baths were applied similarly with isotonic and hypotonic solutions containing 5,000 units of penicillin per cubic centimeter.

The damage to the corneal epithelium due to the anesthetic and the penicillin solution in the two solvents was demonstrated by staining with fluorescein. The entry of fluorescein into the anterior chamber was quantitatively estimated in several instances with the slit lamp, the withdrawn aqueous was compared with standard dilutions of fluorescein.

TABLE 11—*Penicillin Content of Aqueous One Hour After Cathode Iontophoresis, Anode Iontophoresis and Corneal Bath with Solution of Sodium Penicillin Containing 2,000 Units of Penicillin per Cubic Centimeter*

Units Penicillin per Cc Aqueous After		
Cathode Iontophoresis, 2 Ma. for Two Minutes	Anode Iontophoresis, 2 Ma. for Two Minutes	Corneal Bath for Two Minutes
3.2	0.6	0.20
2.4	0.8	0.20
1.6	0.4	0.80
1.6	0.4	0.80
3.2	0.8	0.80
1.6	0.4	0.07
1.6	0.8	0.40
1.6	0.4	0.40
2.4	0.4	0.07
1.6	0.6	0.07
Average 2.08	0.56	0.38

Results Far greater amounts of penicillin were measured in the aqueous when distilled water was used as a solvent instead of a 0.9 per cent solution of sodium chloride (table 12). The drug level was about 22.4 units per cubic centimeter one hour after the iontophoretic application of a strongly hypotonic solution, as compared with 5.3 units per cubic centimeter when a solution of sodium penicillin in saline solution had been applied. With the strongly hypotonic solution the irritation and the haziness of the corneal epithelium were more pronounced. The changes in  $p_H$  were essentially the same in the two types of solutions during the application of the electric current. Because of the lower conductivity of the hypotonic solutions, the impressed potential had to be increased by a few volts.

The effect of the tonicity of the penicillin solutions was also studied in experiments without applying the electric field. The penicillin con-

tent of the aqueous after the two procedures and the results of instillation of fluorescein as observed on the corneal epithelium and in the aqueous are presented in table 13. The drug level in the experiments with hypotonic solutions (8.67 units per cubic centimeter) was about 5.4 times as great as the level achieved with solutions of penicillin prepared in

TABLE 12—*Penicillin Content of Aqueous One Hour After Corneal Iontophoresis at 2 Ma After Five Minutes with a Solution of Sodium Penicillin Containing 2,000 Units per Cubic Centimeter of Distilled Water or 0.9 Per Cent Sodium Chloride*

Units Penicillin per Cc Aqueous After Iontophoresis with Sodium Penicillin Containing 2,000 Units per Cc in	
Distilled Water	0.9% Sodium Chloride
25.6	6.4
12.8	6.4
25.6	3.2
25.6	6.4
19.2	3.2
25.6	6.4
Average 22.4	5.3

TABLE 13—*Penicillin Content of Aqueous and Results of Fluorescein Test One Hour After Corneal Bath with Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter of Distilled Water or 0.9 Per Cent Sodium Chloride*

Units Penicillin per Cc Aqueous After Corneal Bath with Sodium Penicillin Containing 5,000 Units per Cc in		Results of Fluorescein Test			
		On Cornea of Eyes Treated with Penicillin in		On Aqueous of Eyes Treated with Penicillin in	
		Distilled Water	0.9% Sodium Chloride	Distilled Water	0.9% Sodium Chloride
12.8	1.6	+++	++	+++	+
6.4	1.2	++	++	++	+
3.2	1.6	+++	+	+++	+
4.2		+++		+++	
2.4	0.2	++	+	++	+
4.8	0.3	++	+	+++	+
12.8*	3.2*				
12.8*	3.2*				
Average 8.67	1.6				

\* Young rabbit

0.9 per cent sodium chloride (1.6 units per cubic centimeter). This proportion was similar to that determined for the iontophoretically treated animals. For the latter, the individual readings were less erratic. The absolute values recorded in the iontophoresis and bath experiments could not be compared, since solutions of different strengths



were used to obtain readings in a convenient range. The table shows that the intensity of the staining of the cornea with fluorescein at the end of the corneal bath and that of the aqueous observed one hour later roughly paralleled the concentrations of the penicillin in the anterior chamber of such eyes.

**Comment.** It was advisable to investigate several phases of corneal iontophoresis and some factors involved in the clinical method, since the fundamental principles of the procedure were seriously questioned, chiefly on the basis of theoretic considerations. In contrast with the assumption of Hamilton-Paterson,<sup>38</sup> it was shown in experiments 1 and 2 that the sodium salt of crystalline penicillin G has the properties of a good conductor and that the decrease of the hydrogen ion concentration of the saline fluid during corneal iontophoresis with the cup electrode did not cause loss of penicillin activity of practical importance. As mentioned in an earlier paper, the latter observation could not be applied to types of iontophoresis in which the terminal is immersed in very little penicillin fluid.

The various previously described experiments on factors affecting the passage of penicillin through the cornea in iontophoresis did not offer a full explanation of the mechanism by which the electric procedure secured high penicillin levels in the aqueous, although several points were clarified. The interaction of ion transfer (iontophoresis) and the passive transport of the undissociated salt in solution by electro-osmosis is complicated. Penicillin is a strong organic acid with a  $pK$  of 2.7 to 2.8. It can be assumed that in a 0.2 to 0.5 per cent aqueous solution most of the sodium salt is present in a dissociated form and will be transported as such in an electric field. In the later part of the treatment the cornea will carry a negative net charge and the aqueous will be charged positively relative to the cornea. In this period the fluid will be moved electro-osmotically toward the negative pole, which is placed on the cornea, that is, from the anterior chamber outward. It appears, therefore, that only the first of the two electrokinetic phenomena mentioned will be effective in the penetration of penicillin into the eye under the influence of the galvanic current.

Abramson, Moore, Gettner, Gagarin and Jennings<sup>41</sup> stated that a negatively charged, skin-reactive constituent of giant ragweed extract might be introduced by an electric field more efficiently with the positive pole. In view of these results, penicillin iontophoresis from the negative pole was compared with that from the positive pole. The penicillin ion was transferred from the negative pole in an amount

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41 Abramson, H. A., Moore, D. H., Gettner, H., Gagarin, J., and Jennings, L. Isolation of an Unpigmented Skin Reactive Constituent from Extracts of Ragweed Pollen by Electrophoresis, *Proc Soc Exper Biol & Med* **44** 311 (June) 1940.

four times as great as that from the positive pole. It can be concluded from these experiments that penicillin behaves in ocular iontophoresis as a negatively charged ion and that the conditions in iontophoresis of the skin are different from those in corneal iontophoresis.

In addition to other factors, complex diffusion forces are active in iontophoresis, as well as in the corneal bath, when the other experimental conditions are constant. They play a small part in the electric treatment, as the amounts of penicillin determined after the bath present one fourth to one twentieth of the quantities measured in the experiments under the influence of the electric field. This relation varies with the length of the procedure and the strength of the electrolytic solution.

A third group of factors consists of changes in the permeability of the cornea, or rather of the corneal epithelium, due to the procedure. It was shown in earlier experiments that the damaging effect of a local anesthetic on the epithelium has considerable bearing on the level of the drug in the aqueous. From the present study it can be deduced that a five minute flow of the electric current from the cathode through the 0.9 per cent solution of sodium chloride also increases dramatically the corneal permeability to penicillin. On the other hand, the low hydrogen ion concentration in the solution of sodium chloride in the last two minutes of the iontophoresis did not apparently cause an increase in the corneal permeability. The brief and moderate shift in the  $p_H$  of the salt solution was expected to be without influence on the corneal epithelium in view of the investigations of Cogan and Hirsch,<sup>42</sup> who found that "the epithelium maintained its normal barrier properties with variations in the  $p_H$  of 3.5 to 10.2."

The addition of a second salt (sodium chloride) to the solution of sodium penicillin resulted in a steep decrease in the measurable amounts of the antibiotic in the aqueous. Two mechanisms may operate under the conditions of the experiment to bring about this effect. The chloride ions will carry a part of the electric charges, and a smaller number of the penicillin ions will therefore be called on for the flow of the current. As the electric mobility of the penicillin ion is not known, the proportion of the two competing anions which pass through the cornea could not be estimated even if their concentrations were accurately determined. The second mechanism concerns the relation between the tonicity of the bathing solution and the permeability of the corneal epithelium. Solutions of sodium penicillin in distilled water caused a transient diffuse haziness of the corneal surface. Staining of the cornea with fluorescein and diffusion of the dye into the aqueous indicated the extent of the

<sup>42</sup> Cogan, D. G., and Hirsch, E. O. The Cornea. VII. Permeability to Weak Electrolytes, *Arch. Ophthalmol.* **32**: 276 (Oct.) 1944.

epithelial lesion, which could be roughly correlated with the increase of the penicillin level in the anterior chamber. When sodium penicillin in a 0.9 per cent solution of sodium chloride was employed as a bathing fluid on the cornea of rabbits for five minutes, the epithelium generally showed after staining with fluorescein a moderate number of green dots, comparable to those seen after instillation of the anesthetic. The usual concentrations of sodium penicillin in 0.9 per cent solution of sodium chloride are still slightly hypotonic to human tears, the degree of hypotonicity depending on the concentration of the fluid and the potency per milligram of weight of the penicillin salt. When distilled water was used as a solvent, a more extensive lesion of the epithelium could be well demonstrated with fluorescein. The studies of Cogan and Hirsch on the influence of phase solubility of drugs on their penetration through the cornea explained that the penetrability of the lipid-insoluble penicillin salt was greatly increased by the damage to the epithelial barrier.

The increase in the drug level in the aqueous after the use of penicillin in distilled water over that after its use in a nearly isotonic solution of sodium chloride was proportionately similar for the corneal bath and for iontophoresis. It seems, therefore, that in iontophoresis the transient lesion in the epithelial barrier due to the hypotonic fluid is more effective in procuring high drug levels in the aqueous than the relative increase of penicillin ions, which serve as carriers of the current. Further studies on animal and human eyes will show the extent to which the second salt can be omitted in order to improve the efficacy of the iontophoresis or of the corneal bath without causing damage and undue discomfort.

4 *Value of High Drug Levels in the Aqueous After Corneal Iontophoresis or Similar Procedures*—Corneal iontophoresis is one of the nonsurgical methods which achieves a high penicillin level of about 10 to 20 units per cubic centimeter in the aqueous of rabbit<sup>43</sup> and of human eyes<sup>44</sup>. From the depletion curve, it may be assumed that the aqueous of rabbits retains 10 units per cubic centimeter or more of penicillin for several hours after treatment. Whether such a high, but transient, penicillin concentration will be advantageous in treatment of infections of the anterior segment will depend, among many other factors, on the susceptibility to penicillin of the infecting organism and the morbid anatomic character of the lesion. An attempt was made, therefore, to reproduce roughly in *in vitro* and *in vivo* experiments the conditions of such infections of the anterior chamber and to study the effect of varying concentrations of penicillin. In the *in vitro* study, cultures of

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43 von Sallmann and Meyer<sup>1</sup> von Sallmann<sup>37</sup>

44 Wright, R. E. and Stuart-Harris, C. H. Penetration of Penicillin into the Eye, *Brit J Ophth* **29** 428 (Aug.) 1945

*Staph aureus* were exposed to concentrations of penicillin comparable to those in the aqueous, and their viability was observed at various intervals. In the *in vivo* experiments, culture dilutions of the same strain were injected into the anterior chamber of rabbits, treatment with iontophoresis or with corneal bath was initiated eight and twenty-four hours later, and the aqueous was withdrawn after twenty-four hours for plate counts.

**Technic 1** *In vitro* experiments. A strain of *Staph aureus* which was inhibited by 0.1 unit of penicillin per cubic centimeter in the serial dilution assay was used as the test organism. Two-tenths cubic centimeter of a twenty-four hour culture, diluted  $10^{-2}$  in broth, was added to 0.2 cc of the solution of sodium penicillin in broth, so that the series contained 0.5, 1, 5 and 10 units per cubic centimeter. After two and four hours, respectively, the tubes were centrifuged and washed twice with ice cold isotonic solution of sodium chloride. The supernatant was finally replaced by 0.4 cc of broth. The turbidity of the broth was observed after twenty-four and forty-eight hours. Each experiment, consisting of two parallel series and two control series, was repeated five times.

**2** *In vivo* experiments. Both eyes of 9 rabbits were inoculated with 0.05 cc of a twenty-four hour culture of the staphylococcus, strain H, diluted  $10^{-3}$  in a 0.9 per cent solution of sodium chloride. The anterior chamber was inoculated after withdrawal of 0.1 cc of aqueous with approximately 220,000 organisms, as estimated by plate counts. By thrusting a 30 gage needle obliquely through the cornea, leakage from the puncture wound was minimized. After eight or twenty-four hours the right eye was treated by iontophoresis with a solution of sodium penicillin in distilled water containing 5,000 units per cubic centimeter for five minutes at 2 milliamperes. The left eye received a five minute corneal bath with a solution of sodium penicillin of the same strength prepared in a 0.9 per cent solution of sodium chloride. After a twenty-four hour interval, the aqueous was withdrawn, and 0.2 cc of the samples was incorporated in 15 cc of melted nutrient agar for plate count. The course of the inflammation in the differently treated eyes was studied macroscopically and with the slit lamp.

**Results 1** *In vitro* experiments. In the experiments in which the staphylococcus cultures were exposed to penicillin for two hours, growth was noted in all but 1 tube (table 14). In this instance, 1 of the 2 tubes of the series containing 10 units per cubic centimeter was clear. With an exposure to 10 units per cubic centimeter for four hours, 9 tubes with the resuspended organisms remained clear, and 1 had growth at the observation time of twenty-four hours. In the following twenty-four hour period 3 additional tubes became turbid. Five units of penicillin per cubic centimeter prevented visible growth after a four hour exposure in only 1 of the 10 tubes of the series at the twenty-four hour interval. The other experiments with this, or weaker, dilutions of penicillin resulted in full growth of the centrifuged, washed and resuspended cultures.

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**2** *In vivo* experiments. The bacterial counts on the aqueous eight hours after infection showed, with 1 exception, a smaller number of viable organisms in the iontophoretically treated eyes (table 15). Only

in 1 instance were fewer colonies counted in the plate, which was seeded with aqueous from the eye with the corneal bath. The results for another rabbit could not be compared, since the iontophoretically treated eye presented more unfavorable conditions, owing to a corneal burn which was sustained during the procedure.

TABLE 14—*Effect on Cultures of Staphylococcus Aureus of Exposure for Two and Four Hours to Pencillin in Various Concentrations*

Exposure Interval, Hr	Units of Pencillin per Cc	Effects on Cultures * at									
		24 Hour Period					48 Hour Period				
2	0.5	+	+	+	+	+	+	+	+	+	+
	1.0	+	+	+	+	+	+	+	+	+	+
	5.0	+	+	+	+	+	+	+	+	+	+
	10.0	+	+	+	+	±	+	+	+	+	+
4	0.5	+	+	+	+	+	+	+	+	+	+
	1.0	+	+	+	+	+	+	+	+	+	+
	5.0	+	±	+	+	+	+	+	+	+	+
	10.0	—	—	—	—	±	±	±	±	—	±

\* The plus sign indicates growth in two tubes, the minus sign, no growth in two tubes, the plus minus sign, growth in one tube and no growth in second tube.

TABLE 15—*Plate Counts of Aqueous and Degree of Inflammation Thirty-Two Hours After Inoculation of Anterior Chamber with Staphylococcus Aureus Followed After Eight Hours by Iontophoresis with Solution of Sodium Pencillin Containing 5,000 Units per Cubic Centimeter of Distilled Water, or Corneal Bath with Solution of Sodium Pencillin Containing 5,000 Units per Cubic Centimeter of 0.9 Per Cent Sodium Chloride*

Number of Colonies		Degree of Inflammation	
After Iontophoresis	After Corneal Bath	After Iontophoresis	After Corneal Bath
2	9	Moderate	Moderate
9	21	Mild	Moderate
2	21	Mild	Very severe
1	4	Moderate	Severe
0	8	Mild	Severe
3	1	Moderate	Severe
6	6	Moderate	Severe
0	0	Mild	Mild
0	3	Mild	Severe

The effect of one treatment leading to a high peak penicillin level in the aqueous as compared with one treatment securing a medium level could be judged better from the clinical course of the inflammation. In 2 of 9 rabbits no significant difference was noted between the changes in the right and those in the left eyes. The iontophoretically treated

eyes benefited obviously from the high drug level in the 7 remaining instances. These included the eye which was traumatized by corneal burn and injury to the lens capsule during aspiration of aqueous. Under the conditions of the experiment, the advantage of high peak penicillin levels in the aqueous was demonstrated, therefore, by the course of the inflammation and suggested by the bacterial counts on aspirated aqueous.

**Comment** It is known from extensive studies that many penicillin-sensitive organisms survive even after being exposed to the antibiotic substance over a prolonged period. Failures in clinical therapy may be due to this incomplete effect. The correlation between the concentrations of penicillin and its activity was reinvestigated by Rantz and Kirby,<sup>45</sup> who found, in contrast with earlier views, that "under certain circumstances the bacteriostatic activity of penicillin is proportional to its concentration." High peak penicillin levels in the blood, instead of the commonly recommended maintenance of a constant level, are favored for such localized infections as that present in endocarditis lenta.<sup>46</sup> It can be perceived that deeper-seated or less accessible infective lesions in the anterior segment of the eye will also benefit more from high peak drug levels in the aqueous and from a better penetration into the tissue than from a prolonged exposure to low and varying concentrations of penicillin.

The hypothesis that any treatment which secures high drug levels in the aqueous for several hours is of definite advantage is strongly supported by the results of the present *in vivo* and *in vitro* experiments. Injections of staphylococcus cultures into the anterior chamber of the rabbit eye without injury to the lens is sometimes followed by severe iridocyclitis leading to atrophy of the eye, but frequently only by a mild inflammation of self-limiting character. Heavy inoculums of 220,000 organisms did not change these results. For evaluation of the therapeutic effect of one treatment, the inflammatory signs in the first week were, therefore, more important than later observations, especially when additional therapy was employed to save the eyes. The bacterial counts on withdrawn and cultured aqueous are of limited value even in the earlier stages, since the number of organisms in the aqueous is not necessarily representative of the number of surviving organisms in other parts of the anterior chamber.

5 *Palpebral Iontophoresis*—The preceding part of the study pertained mostly to corneal iontophoresis. In the original method of

45 Rantz, L. A., and Kirby, W. M. M. The Action of Penicillin on Staphylococcus *in Vitro*, *J. Immunol.* **48** 335 (June) 1944.

46 Gerber, I. E., Schwartzman, G., and Baehr, G. Penetration of Penicillin into Foci of Infection, *J. A. M. A.* **130** 761 (March 23) 1946.



Wirtz,<sup>47</sup> sponges of cotton gauze were soaked with the electrolyte and were held in direct contact with the surface of the lids, the lid border, the conjunctiva or the cornea. This contact technic has been revived in recent years, and various types of elaborate applicators have been designed, especially for palpebral iontophoresis. They have been widely used for diseases of the lid border, conjunctiva and cornea, and even for deeper-seated lesions of the eye. The technic of palpebral iontophoresis has been advertised as being beneficial also in penicillin therapy, of ocular infections. It was advisable, therefore, to investigate the fundamental principles of this method. Experiments were conducted to determine the content of penicillin in various parts of the lids, conjunctiva, cornea and aqueous after iontophoresis of the lid and simple moist dressings.

**Technic.** An applicator cup, supplied by the Teca Corporation, provided good contact for the cotton sponge on the carefully shaved, closed lids of rabbits. After instillation of 0.1 per cent nupercaine hydrochloride and 2 drops of the penicillin solution in the conjunctival sac, the electrode, containing the sponge soaked with 1.5 to 2 cc. of a solution of sodium penicillin, with a concentration of 5,000 units per cubic centimeter, was held on the closed lids. A current of 2 milliamperes was applied for five minutes to one eye, the second eye was similarly treated for the same length of time but without current (wet dressing). The milliamperage and the timing were selected to permit a comparison with the results of corneal iontophoresis. Immediately after the treatment, the lids were sponged with a 0.9 per cent solution of sodium chloride. The rabbits were killed one hour later. The lids were dissected and separated into an anterior skin-muscle layer and a posterior tarsus-conjunctiva plate. Extracts from the weighed layers of the lids, from the bulbar conjunctiva and from the cornea were prepared by grinding the samples with ignited quartz sand and with phosphate buffer of a  $p_H$  of 6.8. Buffer solution was used also for washing the mortar, pestles and weighing bottles. The extracts and washings were combined in a centrifuge tube and diluted to twenty times the weight of the respective tissues. The tubes were centrifuged, and quadruplicate samples of the supernatant were used for the determination of penicillin by the cup method. Throughout the procedure all materials were kept at a low temperature. Each experiment was repeated six times.

The changes in the  $p_H$  of the penicillin solution in the sponge and the partial inactivation of penicillin by the products of electrolysis were not investigated. A comparative series of experiments was conducted with the same technic, using as the electrolyte sodium sulfadiazine, which is not affected by changes in the  $p_H$ . A 5 per cent solution was applied, and the sulfadiazine content was determined in the various parts of the lids and eyes by the routine procedure of Bratton and Marshall. Each experiment was repeated five times.

**Results.** In the penicillin series, a moderate increase in the drug level was noted after iontophoresis in all tissues except in the conjunctiva bulbi as compared with the level after wet dressings (table 16). It will be remembered that far higher concentrations of penicillin were

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47 Wirtz, R. Die Iontotherapie in der Augenheilkunde, *Klin Monatsbl f Augenh* 46 543, 1908.

obtained in the aqueous with corneal iontophoresis (192 units per cubic centimeter) The amounts of sulfadiazine in the various parts of the eye and its adnexa after iontophoresis of the lid did not exceed, in general, those found in the same structures after wet dressings (table 17) The readings for the cornea were so low and erratic that they could not be evaluated The effectiveness of corneal iontophoresis as compared with that of the palpebral technic is illustrated by the high values obtained with the first method, that is, 119.92 mg of sulfadiazine per hundred cubic centimeters in the cornea and 39.0 mg of sulfadiazine per hundred cubic centimeters in the aqueous

TABLE 16—*Penicillin Content of Parts of the Lids, Conjunctiva, Cornea and Aqueous One Hour After Iontophoresis at 2 Ma for Five Minutes or a Moist Dressing for Five Minutes with a Solution of Sodium Penicillin Containing 5,000 Units per Cubic Centimeter*

Units Penicillin per Cubic Centimeter or Gram				
Lid				
Skin Muscle	Tarsus-Conjunctiva Tarsi	Conjunctiva Bulbi	Cornea	Aqueous
After Iontophoresis				
47.10	8.23	1.90	41.30	0.75
66.10	8.84	6.21	55.40	1.30
50.42	3.96	7.76	70.30	2.00
68.00	5.10	2.32	82.00	1.53
70.00	4.90	1.65	80.70	0.48
57.50	19.20	9.20	105.70	0.63
Average 59.85	8.37	4.84	72.57	1.12
After Moist Dressing				
74.20	1.83	2.83	0.07	0.22
28.30	1.30	6.70	0.07	0.11
38.60	2.83	4.84	66.20	1.99
63.60	8.70	3.60	50.40	1.21
17.30	0.07	1.27	0.07	0.07
68.60	0.07	16.90	72.50	0.89
Average 48.43	2.47	6.02	31.55	0.75

Comment In these experiments on rabbits, little advantage was gained by palpebral iontophoresis with penicillin in regard to the total content of the drugs in the parts of the eye examined It was not possible, however, to study the distribution of the compounds in the various strata of the skin, sweat glands and sebaceous glands The possibility cannot be excluded that the small amounts of the drugs were present predominantly in the glands after application of the electric field, such a distribution is suggested by Rein's<sup>48</sup> investigation of the transfer of colored cations and anions through the skin

<sup>48</sup> Rein, H. Zur Elektrophysiologie der menschlichen Haut, Ztschr. f. Biol. 84:41 (Jan.) 1926

It might be argued that the penicillin was partially inactivated during the iontophoresis of the lid by the decrease of the hydrogen ion concentration in the latter part of the procedure, but the negative results with sulfadiazine iontophoresis indicated that the cause of the inadequate concentration in the tissues lay in the anatomic structure of the lid and conjunctiva and the rich supply of blood vessels

The findings in the present series with sulfadiazine confirm the report of Clark, Strakosch and Nordlum,<sup>49</sup> who studied the passage of sulfonamide compounds through intact skin by iontophoresis and other means of local treatment. They described essentially the same penetra-

TABLE 17—*Sulfadiazine Content of Parts of Lids, Conjunctiva, Cornea and Aqueous One Hour After Iontophoresis at 2 Milliamperes for Five Minutes or a Moist Dressing for Five Minutes with a 5 Per Cent Solution of Sodium Sulfadiazine*

Mg /100 Cc Sulfadiazine				
Lid		Conjunctiva Bulbi	Cornea	Aqueous
Skin Muscle	Tarsus- Conjunctiva Tarsi			
After Iontophoresis				
19 27	Trace	Trace	1 513	Trace
14 35	3 6	6 91	Trace	0
5 17	0 70	Trace	Trace	Trace
31 62		12 2	Trace	Trace
28 62		12 4	Trace	Trace
Average 19 80	1 43	6 302	0 303	
After Moist Dressing				
18 97	0 471	3 33	Trace	Trace
10 13	4 193	6 45	Trace	None
10 71	Trace	Trace	Trace	Trace
32 96		11 61	1 25	Trace
8 42		3 76	4 04	Trace
Average 16 24	1 56	5 03	1 058	

tion for sulfathiazole when applied iontophoretically or by wet dressings to rabbit skin. Even prolonged applications for six hours did not lead to significant differences in the content of the compound with the two types of treatment. In the experiments with penicillin it was not feasible to extend the treatment over long periods because the compound would undoubtedly have been inactivated to a great degree by the alkaline milieu. Since considerably more of the sulfonamide compound was determined in the skin of dead rabbits after the iontophoretic procedure than after wet dressings, it could be assumed that the circu-

49 Clark, W. G., Strakosch, E. A., and Nordlum, C. Penetration of Sulfonamides Through the Intact Skin by Iontophoresis and Other Means of Local Application, *Proc Soc Exper Biol & Med* 50:43 (May) 1942.

lation of blood in the treated area and the barrier qualities of the living epidermis were responsible for the relatively low drug content after iontophoresis in the living animal

*Summary*—1 Sodium penicillin greatly increased the conductivity of electrically pure water and can, therefore, be considered a good conductor.

2 The shift of the hydrogen ion concentration in the penicillin solution beyond a  $p_H$  of 8 in the last one or two minutes of an iontophoretic treatment of the cornea with the usual cup electrode did not inactivate the drug to a degree of practical importance

3 The good penetration of penicillin into the eye under the influence of an electric field was caused by ionic transfer, in addition to an increase in corneal permeability, due to the flow of the current from the cathode and to forces of diffusion

4 Four times as much penicillin was determined in the aqueous one hour after iontophoresis from the cathode than after iontophoresis from the anode This indicated that penicillin at a  $p_H$  of 6 to 8 behaved like a negatively charged ion

5 A low tonicity of the penicillin solution radically facilitated the entry of the drug into the eye both with iontophoresis and with the corneal bath Transient damage to the corneal epithelium, due to the hypotonicity of the bathing fluid, was the main factor in the increased penetration

6 In vivo and in vitro experiments suggest that high peak levels in the aqueous sustained for several hours are desirable in the treatment of severe infections in the anterior segment of the eye

7 Iontophoresis of the lid was only slightly more efficacious than simple wet dressings in obtaining increased and prolonged action of the tested antibiotics in various structures of the lids and the eye Wet dressings may be useful in the treatment of certain surface infections of the lids, conjunctiva and cornea

### III LOCAL INJECTIONS OF PENICILLIN

#### A SUBCONJUNCTIVAL INJECTION

It was previously shown that relatively moderate penicillin levels could be obtained in the aqueous and traces in the vitreous of rabbits by subconjunctival injection if 2,500 units was employed<sup>50</sup> Experimental infections of the vitreous with *Diplococcus pneumoniae*<sup>51</sup> and of the anterior chamber with *Neisseria gonorrhoeae*<sup>27</sup> did not benefit from

50 Struble and Bellows<sup>1b</sup> Leopold<sup>1d</sup> von Sallmann<sup>37</sup>

51 von Sallmann, L Penicillin Therapy of Infections of the Vitreous, Arch Ophth 33 445 (June) 1945

this therapy Clinical reports<sup>52</sup> disclosed that such treatment gave satisfactory results in post-traumatic infections of the anterior segment These observations suggested that beneficial results could be expected whenever the infecting organism was of high susceptibility to penicillin and if the infection had not extended to the lens When strong solutions of penicillin were administered subconjunctivally, the attendant pain and discomfort could be overcome by adding an appropriate amount of procaine Tests carried out in this laboratory confirmed the reports of Hesser and Golland<sup>53</sup> that the action of penicillin was not influenced by the addition of the anesthetic<sup>54</sup>

#### B INJECTION INTO THE ANTERIOR CHAMBER

The tolerance of rabbit eyes to injections of penicillin into the anterior chamber was tested in several laboratories Despite the use of products of various origin and of differences in the technic, the reports showed satisfactory conformity<sup>55</sup> A dose of 0.1 cc of a solution of penicillin containing 2,000 units per cubic centimeter dissolved in 0.9 per cent solution of sodium chloride did not precipitate severe or prolonged reaction in the rabbit eye, provided that the samples were of high or medium purity The penicillin salts manufactured at present in the large pharmaceutical houses can be considered a reasonably safe product when properly handled Clinical experience points to the value of this type of therapy in cases of postoperative or post-traumatic iridocyclitis due to pyogenic organisms<sup>56</sup> Irrigation of the anterior chamber is held to be valuable as a prophylactic procedure in cases of perforating injuries when infection of the anterior segment is probable In treatment of experimental staphylococcal infections of the vitreous, partial success with the method was reported by Leopold<sup>1d</sup> in 4 of 10 eyes Mann<sup>3b</sup> observed striking clinical results in cases of ectogenous infections extending into the vitreous from the replacement of aqueous with a solution of penicillin

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52 Rycroft, B. W. Subconjunctival Penicillin and Intraocular Infection, *Brit J Ophth* **29** 501 (Oct) 1945

53 Hesser, F. P., and Golland, M. Effect of Procaine on Inhibitory Factor of Penicillin, *Mil Surgeon* **98** 47 (Jan) 1946

54 Serial dilutions of procaine hydrochloride containing 4, 2, 1, 0.5, 0.25, 0.125 and 0.06 per cent of the drug were added to appropriate mixtures of cultures of *Staph aureus* in dilutions of sodium penicillin The activity of penicillin was neither increased nor reduced

55 (a) Dunnington, J. H., and von Sallmann, L. Penicillin Therapy in Ophthalmology, *Arch Ophth* **32** 353 (Nov) 1944 (b) Leopold<sup>1d</sup> (c) Mann<sup>3b</sup>

56 Ingalls, R. G. Penetrating Wounds of the Cornea with Hypopyon Treated with Penicillin. A Case Report, *Am J Ophth* **29** 1152 (Sept) 1946

## C INJECTION INTO THE LENS

The advantage of intralenticular injections of penicillin in eyes with the infective focus deep in the lens has been noted experimentally in lesions produced by pathogenic *Staph aureus*<sup>55a</sup> and by strains of *Clostridium welchii*,<sup>57</sup> whereas corneal iontophoresis completely failed to check such infections<sup>58</sup> Intralenticular injections have not been sufficiently used clinically to justify any conclusions as to their effectiveness in the human eye

## D INJECTION INTO THE VITREOUS

It has been shown by several investigators that with injection into the globe adequate amounts of penicillin could be secured in the vitreous A disparity in respect to reports on low penicillin concentrations in the vitreous obtained with other procedures can be accounted for by differences in the dose and in the method of removing the vitreous A slow diffusion gradient of penicillin was demonstrated even in the semifluid vitreous gel of rabbits<sup>59</sup> Samples of fluids aspirated from the vitreous are not representative of the whole, since varying activities can be expected in portions which are obtained before a uniform distribution of the salt has taken place in the gel If the vitreous is removed *in toto* after dissection, admixture of aqueous from the posterior chamber, with a higher concentration of the drug, cannot be avoided However, it is agreed that the low and inconsistent penicillin levels in the vitreous after nonsurgical administration are unsatisfactory The experimental series with high peak levels in the blood or severe inflammation in the posterior segment, as reported in the first part of the present study, confirmed and extended this experience Failures of such penicillin therapy of infections of the posterior segment have been observed both clinically and experimentally

1 *Injection of Crystalline Penicillin into the Vitreous*—The comparatively low toxicity of penicillin rendered the substance suitable for experiments with intravitreal injections<sup>60</sup> Initial stages of experimental infections of laboratory animals and of similar lesions in the human

57 Hoskins, L C Penicillin Therapy of Experimental Infections of the Lens and Vitreous with *Clostridium Welchii*, Arch Ophth **38** 301 (Sept) 1947

58 von Sallmann, L Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infections with *Staphylococcus Aureus* and *Clostridium Welchii*, Arch Ophth **31**.54 (Jan) 1944

59 von Sallmann, L, Meyer, K, and Di Grandi, J Experimental Study on Penicillin Treatment of Ectogenous Infection of Vitreous, Arch Ophth **32**.179 (Sept) 1944

60 von Sallmann<sup>51</sup> Dunnington and von Sallmann<sup>55a</sup> von Sallmann and others<sup>59</sup>

eye<sup>61</sup> were treated successfully with this technic. The use of highly purified preparations was recommended from the first report. The earliest experimental series with penicillin compounds of various purifications—prepared in a small plant—indicated that the impurities in the salts caused a toxic reaction of the inner membranes of the eye.<sup>59</sup> Commercial preparations, which were tested later in this laboratory, were well tolerated by the rabbit eye when the amount of injected penicillin was limited to 100 units. Five times this dose resulted occasionally in circumscribed areas of retinal and choroidal destruction, which were identified only on histologic examination. These laboratory results were contradicted in a recent report of Mann on the deleterious effect of intravitreal injections of penicillin. The author used greater amounts, that is, 1,000 units of penicillin salt from various sources, among them Chas. Pfizer & Co. A batch from this pharmaceutical house was also used in the Knapp Laboratory and was found not to be injurious in lower concentrations. As the lot number of the preparation employed by Mann was not known, it was impossible to trace for more information. The severity and the extent of the chorioretinitis made it improbable that the greater dose of the injected compound produced the destruction. They suggested, rather, a contaminated sample or an unusual number of impurities, such as were present in some of the earlier products. The toxic effects of impurities could have been lessened to some degree by using a more dilute solution. One-hundredth the amount of penicillin administered by Mann controlled experimental infections of the vitreous which had been produced by various strains of pathogenic *Staph. aureus* and one strain of *D. pneumoniae*.<sup>51</sup> To gain more knowledge of the effect of pure preparations, further experiments, including thorough histologic examination of the globes, were conducted with commercial crystalline penicillin and with isolated crystalline penicillin G and crystalline penicillin K.

**Technic.** A 30 gage needle was used to inject 0.05 to 0.1 cc. of the saline solutions intravitreally. Two batches of the "crystalline penicillin sodium," supplied by Commercial Solvents Corporation, were tested, one batch had a potency of 1,430 units per milligram and the other of 1,590 units per milligram (lot no. 46071301). The latter contained 84 per cent of penicillin G. Data on the elementary analysis and on the comparative antibacterial assay were not obtainable. Doses of 200, 1,000 and 5,000 units were administered to 4 or 5 eyes for each concentration. The sodium salt of the isolated crystalline penicillin G (1,600 units per milligram) was prepared by Eli Lilly and Company (lot no. J-85-430). According to the assay of the Rockefeller Institute for Medical Research, the preparation appeared to

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<sup>61</sup> von Sallmann.<sup>51</sup> Feigenbaum, H., and Kornbluth, W. Intravitreal Injection of Penicillin in a Case of Incipient Abscess of the Vitreous Following Extracapsular Cataract Extraction. Perfect Cure, *Ophthalmologica* **110** 300 (Nov-Dec) 1945. Weizenblatt, S. Treatment of Acute Endophthalmitis. Report of a Case, *Arch. Ophth.* **36** 736 (Dec) 1946.

contain about 3 per cent of material occurring in the K region and about 2.3 per cent occurring in the X region. On the preparations of penicillin K the following data were made accessible to us:

Sodium penicillin K (lot no 7 12 46) of Chas Pfizer & Co, Inc			
Elementary analysis			
	Found %	Calculated for $C_{16}H_{25}O_4N_2SNa$ %	
Carbon	52.84	52.73	
Hydrogen	7.07	6.91	
Nitrogen	7.66	7.69	
Potency (based on 1,667 units per milligram for standard penicillin G)			
Turbidimetric assay			Units/Mg
Against <i>Escherichia coli</i>			198
Against <i>Staphylococcus aureus</i>			2,605
Oxford plate assay			
Against <i>Staph. aureus</i>			2,075
Differential assay ratio			
<i>Bacillus subtilis</i> : <i>Staph. aureus</i>			0.36
Sodium penicillin K (lot no RP 310 PI) of the Abbott Research Laboratories			
Elementary analysis			
	Found %	Calculated, %	
Carbon	53.11	52.72	
Hydrogen	6.7	6.9	
Potency			
Against <i>Staph. aureus</i>			2,050
Against <i>B. subtilis</i>			750
Differential assay ratio			0.37

The salts were dissolved in a 0.9 per cent solution of sodium chloride and passed through a bacterial filter. A dose of 2,000 units was introduced in from 4 to 6 eyes.<sup>62</sup>

**Results.** Injections of "crystalline penicillin sodium," Commercial Solvents Corporation. The 14 eyes in which 200, 1,000 and 5,000 units were injected remained clinically free of inflammatory reaction except that caused by the trauma of injection. The following changes were considered of traumatic origin: the damage to the vitreous gel, as described by Loewenstein and Samuels<sup>63</sup> in 1918, the fine, spider-web opacities in the vitreous, probably due to minute hemorrhages, and the few cells circulating in the anterior chamber, with a transient increase in the Tyndall sign. No pathologic change in the fundus could be recognized despite the high dose. The retinal vessels appeared normal in caliber, and the fan of medullated fibers was distinct.

In general, the sections from globes injected with 200 and 1,000 units of crystalline sodium penicillin did not display inflammatory or degenerative lesions of the retina, uvea or optic nerve or damage to the lens. Red blood cells in moderate number in the vitreous were identified as the substrate of the fine, spider-web opacities which were observed clinically in several instances. In some eyes a small number of inflammatory cells and macrophages were seen in the region of the

<sup>62</sup> One sample of crystalline sodium penicillin K and the sodium salt of crystalline penicillin G were made available through the cooperation of the Antibodies Study Section of the United States Public Health Service.

<sup>63</sup> Loewenstein, A., and Samuels, B. Ueber Glaskörperersatz. I. Experimentelle Untersuchungen, Arch f. Ophth. 80:500, 1911.



vitreous base or in other parts of the vitreous, which also contained faintly stained, droplet-like or amorphous debris. It could not be ascertained whether the debris was derived from the injected material. The number of red cells and wandering cells was not greater in the eyes receiving 1,000 units.

The 4 globes which had received the excessive dose of 5,000 units presented the following histologic picture. The anterior segment, including the lens, was free of pathologic change. The vitreous contained at its base, and in 1 instance axially, a few inflammatory cells, macrophages and red blood cells. The number of the cellular elements was not greater than in the eyes which had received 200 and 1,000 units. The retina and the optic nerve of 3 eyes did not show degenerative or inflammatory lesions. In the fourth eye there was a sharply outlined area of retinal atrophy, measuring about  $\frac{1}{2}$  disk diameter, adjacent to the upper margin of the nerve head.

**Injections of crystalline penicillin G and K.** The condition of eyes with 2,000 units of crystalline penicillin G was clinically similar to that of the eyes in the preceding series. A slight flare and a few cells in the anterior chamber and fine, spider-web opacities in the axial part of the vitreous were again ascribed to the trauma of injection. The changes in the aqueous disappeared within one week, and the opacities in the vitreous regressed more slowly.

Histologically, the eyes did not present signs of inflammation, except for an eye with round cell infiltration of the choroid proximal to the needle track. One or two small, circumscribed patches of partial retinal atrophy, of  $\frac{1}{2}$  to  $1\frac{1}{2}$  disk diameters, were visible in each of the 4 eyes. The rods and the outer nuclear and outer plexiform layers were missing here, whereas the elements of the second and third neuron layers and the external limiting membrane appeared intact. The cells of the pigment epithelium beneath the damaged area were partly depigmented or swollen. An apparently normal layer of medullary nerve fibers had prevented the clinical recognition of these small lesions.

The eyes which had received 2,000 units of the first sample of penicillin K presented signs of inflammation which could not have been caused by the trauma (table 18). For several days there were numerous cells in the aqueous and a diffuse veil in the vitreous. These changes were almost absent in the eyes in which the second sample was tested. A characteristic extensive lesion of the fundus was noted in all 6 eyes of this series. The retina was whitish gray twenty-four hours after the penicillin salt had been incorporated, mostly in the quadrant of the fundus which was closest to the point of the needle during the injection. The nerve head was blurred, and small hemorrhages in the retina and vitreous were seen in 3 eyes. The discoloration of the fundus decreased within the first week. At the end of this period grayish islands of

various sizes persisted as remnants of the extensive lesion. Dilatation and marked tortuosity of the retinal vessels were observed in the damaged sectors of the fundi of 3 eyes. With the regression of the grayish appearance of the retina, slightly irregular pigmentation of the eyeground developed in this area, and the fine striation of medullated fibers disappeared, leading to narrowing of the medullary wing in all instances. At this stage the fundus presented, therefore, the picture of a localized chorioretinal lesion with partial atrophy of the optic nerve.

TABLE 18—*Local Toxic Effects Observed After Intravitreal Injection of Commercial Crystalline Sodium Penicillin and the Sodium Salts of Isolated Penicillin G and K*

Type of Penicillin	Potency, Units per Mg	No. of Units Injected	No. of Eyes Receiving Injections	Observation Interval, Weeks	Clinical Observations	Histopathologic Observations
"Crystalline penicillin sodium" (Commercial Solvents Corporation)		200	5		Line, spider web opacities in vitreous, fundus normal	Few inflammatory cells and red blood cells in vitreous
Batch A	1,430			4 12		
Batch B	1,580	1,000	5			
		5,000	4	2 4	Fine, spider web opacities in vitreous, fundus normal	Few inflammatory cells in vitreous, small area of retinal atrophy in one eye
Sodium penicillin G (Eli Lilly & Co.)	1,600	2,000	4	3 4	Fine, spider web opacities in vitreous, fundus normal	Round cell infiltration around needle trace in one eye, small areas of partial retinal atrophy in all eyes
Sodium penicillin K Chas. Pfizer & Co.	2,000	2,000	2	2 4	Fine, diffuse opacities in vitreous, extensive grayish decoloration of retina with vascular changes, followed by circumscribed chorioretinal atrophy and partial optic nerve atrophy	Moderate number of inflammatory cells in vitreous, sectors of complete retinal destruction with obliteration of small retinal vessels and disappearance of medullated nerve fibers
Abbott Laboratories	2,050	2,000	4			

Histologic examination revealed a mild inflammatory response in the form of a moderate number of round cells in various parts of the vitreous. The degenerative changes in the retina were much more extensive than those seen after use of penicillin G and involved all layers. A thin, acellular glial membrane was the only remnant of the retina in several instances, in others, the structure of the inner layers could be identified. Small branches of retinal vessels appeared obliterated, owing to swelling and possible proliferation of the endothelial cells. The seat of the damage was either a broad sector or round areas of several disk diameters near the optic nerve. The pigment epithelium beneath the destroyed retina was depigmented, swollen or proliferated,

and the choroid occasionally showed an inconspicuous accumulation of round cells. In general, the inflammatory changes were negligible in comparison with the severe degenerative lesions of the retina. The histologic picture suggested that the vascular changes accompanied the retinal damage, rather than caused it.

**Comment** The studies on the toxicity of penicillin by intravitreal injection were limited to relatively pure preparations, since nothing could be gained by investigating a great number of the usual commercial preparations, with their changing character. The experiments in this laboratory and those of Mann demonstrated that such batches from the same pharmaceutical concern usually could be well tolerated, or occasionally might produce destructive chorioretinitis. Mann also used crystalline products experimentally without ill effects as far as could be judged ophthalmoscopically, the results of histologic examinations were not reported. It was felt that information about the source, species and quality of the penicillin employed and a careful histologic study of treated eyes were necessary for evaluation and comparison of the data on toxicity. The damage of the retina, choroid and optic nerve with two samples of pure penicillin K was the most remarkable observation in this series, it suggested that some of the circumscribed lesions in the retina previously reported after the use of the common preparations of penicillin may have been caused by the presence of penicillin K in the product. The inferior antibiotic action of penicillin K in comparison with other forms,<sup>64</sup> together with the toxic action of two preparations shown in the present experiments, disqualifies this compound. The moderate toxic lesions in the inner membranes of the eye after the use of penicillin G could also have been caused by the presence of penicillin K in the sample. The low toxicity of this form compared favorably with the results of studies by Van Dyke<sup>65</sup> on penicillin G in general pharmacology.

It was shown that two batches of the commercial product (Commercial Solvent Corporation), "crystalline penicillin sodium," were noninjurious to the rabbit retina when a dose of 1,000 units was injected into the eye. Five times this amount also did not cause damage except for a small area of chorioretinal atrophy in 1 eye. With present knowledge, intravitreal injection of commercial crystalline penicillin with a fine needle (30 gage) can be considered as an effective and

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64 Eagle, H., and Musselman, A. Low Therapeutic Activity of Penicillin K Relative to That of Penicillins F, G, and X and Its Pharmacological Basis, *Science* **103** 618 (May 17) 1946. Coghill, R. D., Osterberg, A. E., and Hazel, G. R. The Relative Effectiveness of Pure Penicillins G, X, and K, *ibid* **103** 709 (June 14) 1946.

65 Van Dyke, H. B. Pharmacological Observations on Crystalline Sodium Penicillin, *Proc Soc Exper Biol & Med* **56** 212 (June) 1944.

reasonably safe procedure in treatment of severe infections of the vitreous

Summary 1. Careful histologic examination proved that 2 samples of commercial crystalline penicillin could be injected into the vitreous up to amounts of 1,000 units without causing any retinal lesions. A minimal retinal damage was noted in 1 eye with the highest concentration, of 5,000 units.

2. One sample of crystalline penicillin G (2,000 units) was administered intravitreally, with a moderate toxic effect, which could be recognized histologically.

3. Two batches of crystalline penicillin K (2,000 units) produced severe degenerative changes in the retina and optic nerve when injected into the vitreous. It can be assumed that the destructive effect was produced by the penicillin compound, and not by residues of agents used for its isolation.

2 *Intravitreal Injection of Penicillin and Antitoxin*—In a previous paper<sup>58</sup> it was noted that inflammatory changes in the posterior segment of the globe frequently led to the development of strands in the vitreous after the staphylococcic infection had obviously been checked by penicillin. Retinal folds, either circumscribed or amounting to extensive retinal detachment, were ascribed to the traction of these strands. It was assumed that the continued presence of preformed bacterial toxins might have aggravated the residual inflammation, although the organisms probably had been eliminated.

On the basis of this assumption, the clinical and histologic changes produced by injecting staphylococcus exotoxin were studied in preliminary experiments. These were followed by attempts at topical treatment with penicillin combined with homologous antitoxin. The effect of the combined treatment was compared with that of treatment with penicillin alone. The investigation was extended to local treatment with penicillin and antitoxin of vitreous infections with *D. pneumoniae* type III.

Technic. The staphylococcus toxin was prepared, and its hemolytic and necrotizing properties were tested, as described in the experiments in the first part of this paper. Injections of 0.05 to 0.1 cc. of the filtrate were made into the vitreous. Most of the 10 eyes were observed for twelve weeks.

Rabbits were immunized in accordance with general practice with a toxin derived from the same strain of *Staph. aureus* BD as was used for the ocular infections. The antitoxin titer of the serum was tested at suitable intervals, serums with titers of 13, 19 and 20 antitoxin units per cubic centimeter were finally employed for treatment after passage through a diatomaceous filter. A preservative was not added. The intravitreal therapy consisted in the injection of 0.1 cc. of a solution which contained 100 units of penicillin and 10 to 18 antitoxin units. The control eyes received 100 units of penicillin. The solutions were administered six hours (in 3 rabbits), eight hours (in 5 rabbits) and twenty-four hours (in 6 rabbits).

after injection of 0.05 cc of *Staph aureus* BD in a  $10^{-3}$  to  $10^{-4}$  dilution of a twenty-four hour broth culture

Pneumococcus antitoxin in rabbit serum, with a titer of 458 micrograms of antibody nitrogen per cubic centimeter, was supplied by the laboratory of Dr M Heidelberg, department of medicine, College of Physicians and Surgeons. The "merthiolate" preservative was dialyzed against 0.9 per cent sodium chloride, and the serum was then passed through a microfilter under centrifugation. The infection of the vitreous of 6 eyes was made with 0.1 cc of a  $10^{-3}$  dilution of a strain of *D pneumoniae* type III<sup>66</sup> and was inhibited by 0.0125 unit of penicillin per cubic centimeter. The treatment consisted in injecting the same dose of penicillin (100 units) as that used in the experiments with staphylococcal infection eight hours after inoculation. The dose of the antitoxin-penicillin fluid had a titer of about 0.4 microgram antibody nitrogen.

**Results.** Acute uveitis followed the injection of the staphylo toxin into the vitreous. The inflammatory signs in the anterior segment subsided after several weeks, posterior synechias or partial occlusion of the pupil remained. With the exception of 1 eye, posterior cortical cataract developed. Strands in the vitreous, partial or total retinal detachment and atrophy of the medullated fibers were seen clinically in the later stages, when the diffuse cloudiness had disappeared from the vitreous. The histologic study revealed strands of vitreous in 8 of the 10 globes. The strands varied from delicate to heavy and were often anchored to the retina around the disk or in a peripheral area. There were observed either steep retinal folds or total or partial retinal detachment, obviously produced by shrinkage of the membranes. The destruction of the retina was in most instances widespread and involved either all retinal layers or the neuroepithelium predominantly. The nerve had been affected by the traction of the strands to a variable degree. The presence of posterior cortical cataract was confirmed histologically. Foci of inflammatory cells remained in the ciliary body or the choroid of 3 eyes.

When treatment was initiated six hours after injection of the culture of staphylococci, the infection was controlled in the 3 eyes treated with penicillin and antitoxin, as well as in the 3 eyes treated with penicillin alone. No essential difference between the two groups was noted histologically. In the short interval between inoculation and treatment no strands developed in the vitreous. Inflammatory cells were present in moderate numbers three to four weeks after each type of therapy.

In the eyes treated eight hours after inoculation, the infection was not checked in 1 of 5 eyes with penicillin therapy, and in 2 of 5 eyes with the combined therapy. One of the eyes successfully treated with penicillin and antitoxin had severe optic neuritis, and 2 had fine strands

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<sup>66</sup> The lyophilized culture (36321) was obtained from the New York State Department of Health, which furnished the following data. The strain was isolated from a specimen of pus from a patient with acute mastoiditis, and its virulence for rabbits was demonstrated by intravenous injection.

in the vitreous. One of the eyes treated with penicillin alone also showed formation of strands.

Panophthalmitis with perforation or an abscess in the vitreous developed in the 12 eyes in which treatment was delayed twenty-four hours. Panophthalmitis with early perforation occurred in 4 of the eyes treated with penicillin and in 2 of the eyes treated with penicillin and antitoxin. The rest of the globes showed clinically and histologically the picture of an abscess of the vitreous.

The endophthalmitis in the 6 eyes into which were injected *D. pneumoniae* and which were treated after eight hours generally ran an unfavorable course. Five weeks after treatment extensive inflammatory changes were observed in all eyes, and foci of round cells were seen in the uvea. Shrinking membranes in the vitreous led partly to retinal detachment or to inward displacement of the nerve head. These lesions were more pronounced in the eyes treated with penicillin and antitoxin.

**Comment.** The combined action of antitoxin serums and penicillin was studied in infections with various toxin producers, the antibiotic being directed toward inhibition of the growth of the offending organism and the antitoxin to neutralization of the toxin formed. Encouraging results of this therapy were reported in cases of gas gangrene<sup>67</sup> and of diphtheria.<sup>68</sup> The resemblance of the endophthalmitis produced by staphylococcus toxin to the lesions present in the vitreous and retina after effective penicillin therapy of staphylococcic infections suggested the combining of penicillin with specific antitoxin serums. The results were unfavorable. In none of the three groups of the staphylococcic infections was the course of the inflammation significantly altered by the combined treatment. It may be that the introduction of the serum as an excellent nutritive agent counteracted a possible beneficial effect.

In the tentative experiments with pneumococcic endophthalmitis the results were even less satisfying with penicillin and antitoxin than with penicillin alone. The infection with the strain of *D. pneumoniae* used in this series responded less favorably to penicillin than the strain which had been employed in a previous experimental series. As the

67 McIntosh, J., and Selbie, F. R. Combined Action of Antitoxin and Local Chemotherapy on *C. Welchii* Infection in Mice, *Lancet* **2** 224 (Aug. 21) 1943. Evans, D. G., Fuller, A. T., and Walter, J. New Drugs Active in the Chemotherapy of Experimental Gas Gangrene, *ibid.* **2** 523 (Oct. 21) 1944. Siebenmann, C. O., and Plummer, H. Chemotherapy and Antitoxin Therapy of Experimental *C. Welchii* Infection in Mice, *J. Pharmacol. & Exper. Therap.* **83** 71 (Jan.) 1945.

68 Ercoli, N., Lewis, M. N., and Moench, L. J. The Antibacterial Activity of Penicillin in Experimental Infections of Mice with *C. Diphtheriae*, *J. Pharmacol. & Exper. Therap.* **84** 120 (June) 1945. Young, R. G., and Mood, G. M. Effect of Penicillin on Infection of Guinea Pigs with *Corynebacterium Diphtheriae*, *J. Bact.* **50** 205 (Aug.) 1945. Long, D. A. Penicillin and Diphtheria, Correspondence, *Brit. M. J.* **1** 773 (May 18) 1946.

susceptibility of the former to penicillin was greater than in the older series, the larger inoculum (0.1 of a  $10^{-1}$  dilution, instead of a  $10^{-2}$  dilution) may have resulted in the unsatisfactory course

Summary. 1 Injections of staphylococcus toxin into the vitreous of rabbits produced lesions similar to those observed in eyes treated successfully with penicillin

2 Intravitreal injections of a mixture of a homologous antitoxin and penicillin were no more beneficial to the course of an experimental staphylococcic infection than was treatment with penicillin alone

3 An endophthalmitis caused by *D. pneumoniae* type III reacted less favorably in tentative experiments to injections of penicillin and antitoxin than to penicillin alone

#### IV GENERAL CONCLUSIONS

The present study extended over several phases of the parenteral and local use of penicillin in ophthalmology. The failure of penicillin to pass the blood-aqueous barrier in adequate amounts during systemic therapy could not be related to a selective transfer through the ciliary epithelium or to a restraining effect of the epithelial membrane, it was shown, rather, to be related to the functional states of the capillary wall, to the steep decrease in the drug level in the blood by rapid renal excretion and, in a moderate degree, to the speed of absorption of the substance from the aqueous

The negligible role of the ciliary epithelium in the mechanism of the passage of penicillin across the barrier was demonstrated by inhibiting the cyanide-sensitive respiratory enzyme system and was further suggested by the distribution of penicillin between blood and aqueous when renal clearance was prevented. The latter experiments also pointed to the value of a high and sustained penicillin content of the blood in securing satisfactory concentration of the drug in the aqueous. The importance of capillary permeability was shown by the great change in the aqueous-blood ratio of penicillin in various stages of a non-bacterial endophthalmitis

In view of these experimental results, there is reason to believe that the best opportunity for utilizing the benefits of systemic penicillin treatment of severe ocular infections is offered in the administration of massive doses in the acute stages, aided by the simultaneous local instillation of vasodilators in cases of less violent inflammations, as an adjuvant may be considered the use of substances which decrease the renal output of the antibiotic by competing for the same excretory mechanism. General treatment may effectively supplement local penicillin therapy when the infective foci are not easily accessible by local methods

In the study of the surface application of penicillin, the continuance of penicillin activity was usually observed in the tears for eight hours after one instillation of drops or ointment, suggesting that the frequency of treatment of external infections can be reduced without excessive tearing or secretion

Several aspects of ocular iontophoresis with penicillin were studied. The claims of poor conduction of the compound and of a substantial destruction of the antibiotic by the shift of the hydrogen ion concentration, due to the products of electrolysis, were disproved in regard to corneal iontophoresis with applicator tubes of sufficient capacity. It was shown that the high penicillin content of the cornea and aqueous was procured by the effect of the flow of the current from the cathode on the barrier properties of the epithelium, by ionic transfer and, in a small part, by forces of diffusion. When solutions of low tonicity were employed, much more of the substance was observed in the aqueous, both after iontophoresis and after corneal bath, owing, however, to damage to the corneal epithelium. Palpebral iontophoresis with penicillin was far less valuable in achieving high drug levels in the anterior segment of the eye than was the corneal technic, in fact, little advantage was gained by the electric procedure as compared with the use of moist dressings

It was of general interest to determine whether transient high peak concentrations of penicillin were advantageous in controlling infections of the anterior segment. In vitro and in vivo experiments gave evidence that better results could be expected from such high drug levels when the infecting organism was of medium sensitivity to penicillin. The observations appear applicable to iontophoresis, as well as to other means (cotton packs, injections) of obtaining a high penicillin content in the eye

The usefulness of intraocular injections of penicillin had been shown previously in this and in other laboratories. The experimental results were verified by the clinical reports of several authors. The superiority of introducing the compound directly into the vitreous in treatment of infections of the posterior segment was demonstrated in experimental animals. The present painstaking investigations were concerned with the toxicity of excessively high doses of a commercial crystalline penicillin and of crystalline penicillin G and penicillin K, when injected into the vitreous space. A dose equivalent to 1,000 units of the commercial crystalline penicillin was used, without causing histologically recognizable retinal lesions. With a dose equivalent to 5,000 units of the commercial crystalline penicillin, a small, circumscribed area of chorio-retinal atrophy was seen histologically in but 1 of all the serially sectioned eyes. A dose of 1,000 units is about ten times the amount which was effective in checking various experimental infections of the vitreous



Injection into the vitreous of 2,000 units of one sample of isolated crystalline penicillin G gave rise to small lesions of the outer layers of the retina. When 2,000 units of the isolated crystalline penicillin K was injected, there was severe damage of the retina in all eyes, leading to localized retinal destruction and partial atrophy of the optic nerve. Penicillin for intraocular use, therefore, should be sterile, highly purified and relatively free of penicillin K. With observance of these requirements and the necessary technical care, direct injections of penicillin in the vitreous can be considered at present the most reasonable treatment of infections of the posterior segment.

Most of the data reported here were obtained in experiments on rabbits and were referred to common physiologic mechanisms. They may be correlated cautiously to conditions of the human eye so far as the fundamental concepts are concerned, but no conclusions can be drawn in regard to the quantitative data. A growing number of observations on the human eye corroborate some experimental findings, but more evidence, provided by well observed cases, is desirable to confirm or to disprove the clinical applicability of other experimental deductions.

NOTE—Since this study was completed, an article by Sorsby and Ungar,<sup>69</sup> entitled "Pure Penicillin in Ophthalmology," has appeared.

The studies on the toxic effect of crystalline penicillin on the retina were extended to the types F and X and were amplified with respect to commercial penicillin. These experiments were not included in the original paper, for they had not been completed at the time of its submission. Penicillin F was available in such a small quantity that the injected dose had to be reduced to 1,000 units. Penicillin X was tested in the usual dose of 2,000 units and in the massive dose of 5,000 units. The experiments with commercial penicillin were completed by using 2,000 units. The technic of injection was the same as that previously described. The following data were available on the analysis of the two species of penicillin.

Penicillin X, pure, not crystalline (lot no 76929) of Lederle Laboratories Division, American Cyanamid Company

Elementary analysis not obtainable

Differential assay ratio (*B. subtilis* to *Staph. aureus*)

1.2

Penicillin F crystalline (lot no 123 Bel 4) of The Upjohn Company

Chemical Analysis	Found	Calculated from $C_{14}H_{18}O_4N_2SNa$
Carbon, per cent	59.85, 50.118	50.28
Hydrogen, per cent	5.86, 6.08	5.73
Nitrogen, per cent	8.49, 8.41	8.38
Double bonds	1.02	1.00
Biologic assays		
Potency		Units/Mg
Against <i>Staph. aureus</i>		1,625
Against <i>B. subtilis</i>		1,075
Differential assay ratio	0.66	

69 Sorsby, A., and Ungar, J. Pure Penicillin in Ophthalmology, Brit. M. J. 2:723 (Nov. 16) 1946.

The distribution curve (Dr Lyman Craig, of the Rockefeller Institute for Medical Research) indicated that this material was free from penicillins X and K. A small deviation on the graph might be interpreted as indicating a small per cent of penicillin G.

The results are presented in table 19, in which the data on the previous series are also given. It is evident that penicillin F did not cause any damage to the retina or other parts of the interior of the eye when 1,000 units was introduced. Penicillin X was well tolerated in the dose of 2,000 units. Circumscribed lesions of the retina, as observed with the preparation of penicillin G used in this series, were absent. When the dose of penicillin X was increased to 5,000 units, there was a localized area of injury in the neuroepithelium in 1 of 4 eyes. The retina was unchanged after injections of 2,000 units of commercial

TABLE 19—*Effect of Intravitreal Injection of Penicillins G, F, X and K and of Commercial Crystalline Sodium Penicillin on Retina of Rabbits*

Penicillin Preparation	Dose Injected, Oxford Units	Number of Eyes	Days of Observation	Appearance of Retina
Penicillin G	2,000	4	21-28	Small, circumscribed lesions on neuroepithelium in 4 eyes
Penicillin F	1,000	4	20-24	Normal
Penicillin X	2,000	4	7-31	Normal
	5,000	4	7-31	Normal in 3 eyes, small circumscribed lesions in neuroepithelium in 1 eye
Penicillin K (2 batches)	2,000	6	10-28	Extreme and extensive destruction of retina in 6 eyes
Commercial crystalline sodium penicillin	200	5	24-60	Normal
Batch 1	1,000	5	24-60	Normal
Batch 2	2,000	4	10-28	Normal
	5,000	4	10-28	Normal in 3 eyes, small circumscribed lesions in 1 eye

crystalline sodium penicillin, a result which was expected from the infrequent occurrence of small lesions when 5,000 units had been used.

So far as may be concluded from the use of only one or two preparations of the various species of penicillin and of the commercial salt, penicillin X is the least toxic, but penicillin F cannot be included in this comparison, since it was introduced in a dose of only 1,000 units. The results with "crystalline penicillin sodium" of the Commercial Solvents Corporation compared favorably with those for penicillin X. It was recently shown that the antibacterial activity of the pure penicillin is lower than that of the impure preparations.<sup>70</sup> Even if the pure species were available for clinical use no advantage would be

<sup>70</sup> Hobby, G. L., Burkhart, B., and Hyman, B. Chemotherapeutic Action of Various Forms of Penicillin on Hemolytic Streptococcal Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **63**: 296 (Nov.) 1946.

gained over treatment with commercial crystalline penicillin. If a high grade of this penicillin can be obtained and assurance can be given that it is practically free of penicillin K, the intravitreal treatment of infections of the posterior segment of the eye seems a safe procedure.

Dr. Dan H. Moore made the measurements of conductivity on a solution of penicillin G, and Miss P. Pfaff made serial preparations of 40 eyes in which penicillin was injected intravitreally.

The United States Public Health Service, National Institute of Health, Bethesda, Md., provided samples of penicillin G, F and K, the Abbott Laboratories supplied a preparation of penicillin K, the Lederle Laboratories Division of the American Cyanamid Company supplied the sample of penicillin X, the Commercial Solvents Corporation donated the preparation of "crystalline penicillin sodium," and the Teca Corporation constructed an application cup for contact iontophoresis in rabbits.

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# CATARACT EXTRACTION BY THE SUCTION METHOD

A Review of Seventy-Five Cases

CHARLES I THOMAS, M D

CLEVELAND

THERE is a great amount of literature available regarding the efficiency of the various types of cataract extraction. Although operators who have adhered to one method do not change easily, there should be more flexibility in the surgical technics used and emphasized in present day surgery. Though the procedure of cataract extraction is a matter of the individual surgeon's training, there are types of cataracts which are more efficiently removed by one method than by others. One can even say that it may be necessary to try several types of extraction on one lens in order to remove it as desired. Blaess<sup>1</sup> stated that individualism in surgical work is greatly overrated. It is more important to make the proper application of the technic most suitable to the case in question. I wholeheartedly agree with this opinion. The surgeon should adapt his methods to the case presented, having several procedures at his command and possessing the surgical judgment and flexibility befitting the occasion.

The intracapsular removal of the crystalline lens by means of the suction instrument has not yet been given its proper place of importance in cataract surgery. It is an extremely useful method, and one that is quite needlessly feared by many ophthalmic surgeons. Careful study of case reports by Nugent,<sup>2</sup> Wright,<sup>3</sup> Castroviejo,<sup>4</sup> Wolfe<sup>5</sup> and me

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1 Blaess, M J Removal of Cataract by Aspiration, *Arch Ophth* **19**:902 (June) 1938

2 Nugent, O B Cataract Extraction, *Texas State J Med* **32**:664, 1937, Oral Vacuum Control Valve and Modified Green's Suction Cup, *Tr Sect. Ophth, A M A.*, 1933, p 307

3 Wright, R E Cataract Extraction by the Barraquer Method, *Brit J Ophth* **9** 57, 1925, The Barraquer Operation and Vitreous Changes, *Am J Ophth* **7** 155, 1924

4 Castroviejo, R Theoretical and Practical Study of the Intracapsular Cataract Extraction, *Am J Ophth* **15**:406, 1932

5 Wolfe, O R The Barraquer Cataract Extraction, *Am J Ophth* **18** 556, 1935

fails to show any increase in risk to the patient by employment of this method. It should not be a routine procedure in all lens extractions, but it is extremely useful in the proper case. Every instrument table should have the necessary equipment to make this extraction possible. It has been found that, with this routine, intracapsular extraction has been made possible on many occasions when forceps extraction would have failed. One should also realize that the method to be used in intracapsular extraction may not be decided on until the anterior chamber has been opened and the character of the lens capsule studied. Then the surgeon should choose the method of extraction most likely to accomplish his purpose favorably.

#### HISTORY

The suction method, as it is today, evolved from an aspiration procedure by means of a hollow needle for removal of the contents of the lens. It was not until the twentieth century that a flat disk was attached to the aspiration needle in order to apply suction to the lens capsule and remove the cataract in its entirety. Antyllus,<sup>6</sup> during the Greek-Roman period (156 B. C.—576 A. D.), Tsabet ben Corra,<sup>7</sup> in the ninth century, and Alcoatín,<sup>8</sup> in the twelfth century, mentioned the removal of cataract by means of suction, but the method was applied to the cataracts of soft or liquid consistency which could be aspirated with the hollow needle. With the advent of the work of Daviel<sup>9</sup> and Brisseau,<sup>10</sup> this procedure fell into disuse to be revived and modified a century later as a method of intracapsular extraction. Early in the twentieth century, Herz<sup>11</sup> introduced his suction cup, generating suction by means of the mouth, and Stoewer<sup>12</sup> devised a similar instrument, with which, however, suction was obtained by means of a rubber ball. Other models were made by Hulen,<sup>13</sup> Fisher,<sup>14</sup>

6 Antyllus, cited by Garrison, F. History of Medicine, Philadelphia, W. B. Saunders Company, 1929.

7 Tsabet ben Corra, cited by Ribeiro<sup>21</sup>

8 Alcoatín, cited by Ribeiro<sup>21</sup>

9 Daviel, M. Sur une nouvelle methode de guerir la cataracte par l'extraction du cristallin, *Mem Acad roy de chir* 2: 337, 1753.

10 Brisseau. Les recherches sur l'origine et les progres de la chirurgie, Paris, G. Cavelier, 1734, p. 204.

11 Herz, cited by Saint-Martin, R. L'extraction capsulo-lenticulaire de la cataract, Paris Masson & Cie, 1935.

12 Stoewer, P. Demonstration eines Instrumentes zur Extraction der Linse in der Kapsel, *Ophth Gesellsch* 30: 296, 1902.

13 Hulen, V. H. Vacuum Fixation of the Lens in the Extraction of a Cataract in Its Capsule, *Tr Sect Ophth, A. M. A.*, 1911, p. 73.

14 Fisher, W. A. Present Status of Intracapsular Cataract Operation, *Illinois M J* 65: 437, 1934.

Crosley<sup>15</sup> and Cruickshank<sup>16</sup> In 1916 Barraquer<sup>17</sup> made his contribution of the cresiphake This suction instrument was motor driven, and, as Barraquer stated, consisted of "a pneumatic forceps and a zonulatomer" This instrument was adopted by various surgeons throughout the world, and modifications of the apparatus were then made by Dimitry,<sup>18</sup> Rochon-Duvignaud<sup>19</sup> and Arruga<sup>20</sup>

By its development through the centuries, as so appropriately stated by Ribeiro,<sup>21</sup> "aspiration has triumphed It is useful and in some cases indispensable"

#### INDICATIONS FOR THE SUCTION TECHNIC

The suction method can be used to the greatest advantage in cases in which (1) the lens is hypermature, (2) the capsule is tense, (3) the capsule has exfoliated, (4) the lens must be dislocated before it is tumbled or slid out of the fossa or (5) the capsule is friable and will not stand any tension

*Hypermature Lens*—When this condition is encountered, the extracapsular method of extraction is adequate, and has certainly stood the test of time, but if the intracapsular method is to be used, the suction method is ideal In such a condition the lens capsule is usually tight and swollen, and ruptures easily if the forceps grasps it When this type of lens is encountered, the suction cap, with its more evenly distributed traction on the capsule, offers the best method of removal of the lens

*Lens with Tense Capsule*—In another group of cataracts, the picture of hypermature lens is not present, but the capsule is tight and cannot satisfactorily be grasped with the capsule forceps without the probability of rupturing the capsule Such lenses are ideally removed by application of suction This condition is apt to occur in the younger

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15 Crosley, E R Intracapsular Extraction by the Vacuum Cup Method Report of Fourteen Cases, Illinois M J **63** 519, 1933, Intracapsular Cataract Extraction by the Vacuum Cup Method, Am J Ophth **15** 1147, 1933

16 Cruickshank, M M Phacoerisis, Brit J Ophth **9** 321, 1925

17 Barraquer, J A Quelques indication de la phakoerisis, Clin opht **22** 387, 1917, Phakoerisis, Arch Soc oftal hispano-am **17** 252, 1917, Dangers of Capsulotomy and Advantages of Complete Extraction, Arch Ophth **50** 307 (July) 1921, Phakoerisis, *ibid* **51** 448 (Sept) 1922

18 Dimitry, T J Vacuum Grasping Instrument for the Removal of Cataract in Capsule, Arch Ophth **9** 261 (Feb) 1933

19 Rochon-Duvignaud, cited by Saint-Martin, R L'extraction capsulo-lenticulaire de la cataract, Paris, Masson & Cie, 1935

20 Arruga, H Extracción intracapsular de la catarata, Arch de oftal hispano-am **30** 593, 1930

21 Ribeiro, R La aspiracion al servicio del tratamiento de la catarata a traves de los siglos, Arch Soc oftal hispano-am **5** 434, 1945

type of cataract, in which a tight zonule may be present. These zonular fibers are difficult to rupture, and the traction and counterpressure necessary to rupture the fibers are often so great that the capsule may, and often does, rupture before the zonule when the capsule forceps is applied. Hence, with application of the suction method tension is more evenly distributed on the capsule, with less likelihood of rupture.

*Exfoliation of the Lens Capsule*—This condition requires removal of the lens, preferably by the intracapsular route. Owing to the degenerative changes that take place in the lens capsule, this structure disintegrates readily when attempts are made to grasp it with the lens forceps (Vogt,<sup>22</sup> Sobhy Bey<sup>23</sup>). The suction instrument, adhering to a larger area and distributing its lines of stress over a large area, is more likely to bring the lens out intact than is the capsule forceps. Because of the frequency of glaucoma capsulare (Sobhy Bey,<sup>23</sup> Vogt,<sup>22</sup> Busacca<sup>24</sup>), removal of all the capsular fragments is advisable, so whenever possible an intracapsular operation should be performed.

*Aid in Dislocation of Lens*—In delivering the lens with the capsule forceps, it has been found useful first to dislocate the lens by means of the suction cup placed in the center of the lens and then to reapply the capsule forceps. This is applicable when the operator feels that the tension on the capsule is not causing sufficient progress in dislocation or when he believes that rupture of the capsule is imminent.

*Friable Lens Capsule*—Another type of cataract for which the suction method is applicable is the senile nuclear and cortical cataract with a friable capsule. It is apparent at the outset that as soon as the capsule is grasped it will stand no tension. With these cataracts, if one prefers the intracapsular operation, the suction method is ideally applied.

#### ADVANTAGES OF THE SUCTION METHOD

According to Barraquer, there are three defects in the extracapsular method of extraction: (1) the necessity for pressure and its consequences, (2) instrumentation with the eye, to remove the remains of the lens, and (3) the retention of cortical material. He reasoned that any method by which the lens is removed without pressure and excessive instrumentation is the safest means of avoiding complications. On this principle, the author based the two advantages of the suction

22 Vogt, A. Neue Fälle von Linsenkapselglaukom (Glaucoma capsulare), Klin Monatsbl f Augenh **84** 1, 1930.

23 Sobhy Bey, M. A Contribution to the Study of Exfoliation of the Lens Capsule or Glaucoma Capsulo-Cuticulaire with Anatomical Preparation, Brit J Ophth **16** 65, 1932.

24 Busacca, A. Anatomische und klinische Beobachtungen über die Zonulalmelle und ihre Ablösung von der Linse, Klin Monatsbl f Augenh **83** 737, 1929.

apparatus for removal of the lens over the capsule forceps, namely, the evenness of traction, and less counterpressure

The drawing of the suction tip in place on the capsule of the lens (fig 1) shows the lines of traction magnified and illustrates the large area over which this pull is exerted. This method not only lessens the likelihood of rupture of the capsule but also affords an easier removal of the lens itself by distributing the area of traction. This drawing may be compared with figure 2, showing the lines of traction on the lens capsule when the capsule forceps is used. Here, the entire weight of the lens and its attachments are suspended from a relatively small area

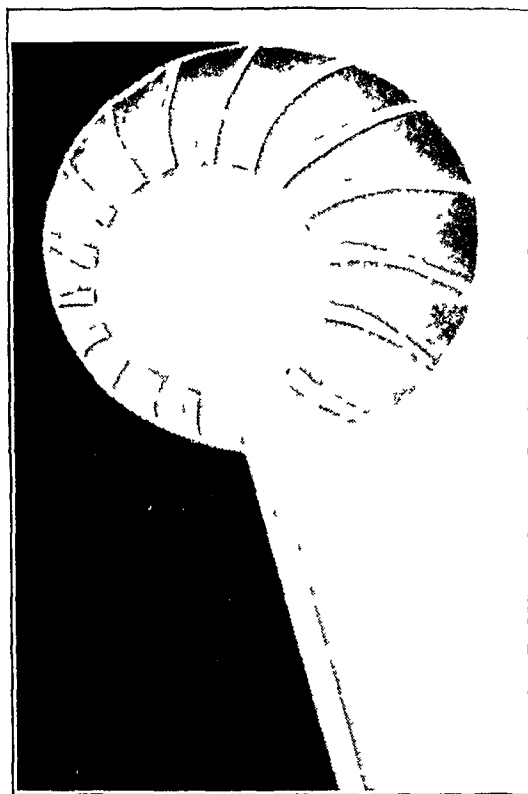


Fig 1—Suction tip in place on the lens capsule, showing lines of stress

The second advantage, that of less counterpressure, is based on the evenness of traction, and, consequently, the necessity of less pressure to produce the same effect. In one of the cases studied, this advantage was strikingly illustrated, as early in the extraction a bead of vitreous presented at the edge of the wound behind the lens but was not forced out because no counterpressure was necessary, and the lens was delivered by means of suction only. Immediate closure of the wound after the lens was removed prevented any complication.

#### PITFALLS IN USE OF THE SUCTION TECHNIC

Besides emphasizing the advantages of removal of the lens by suction, I wish to mention the pitfalls in this operative procedure and



to list the types of cases in which it is contraindicated. The pitfalls lie, first, in the improper selection of cases in which the method is to be used and, second, in loss of vitreous as a result of improper selection of cases, improper choice of instrument or faulty application of the technic. Proper selection of cases on the basis of the indications discussed earlier in the paper should be followed in order that the best results may be obtained. Loss of vitreous is often mentioned as a frequent occurrence. This complication should not be feared, however, if cases are selected properly and the instrument is applied with precision. I believe that the likelihood of loss of vitreous is much greater with motor suction than with the syringe type. The instant that the

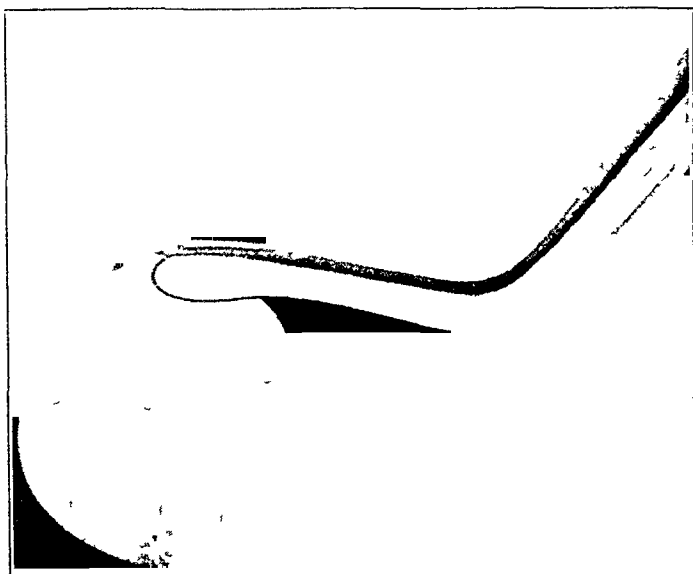


Fig. 2—Capsule forceps in place on the lens capsule, showing lines of stress

disk slips from the capsule the suction is relaxed, whereas with motor suction another manipulation is required to stop the pull.

There should be less chance for loss of vitreous when suction is used under proper conditions than when the capsule forceps is used for intracapsular extraction. With the use of the capsule forceps, counterpressure is an important manipulation in bringing about the removal of the lens, and it is because of this procedure that vitreous is often lost. With the suction technic counterpressure is a relatively unimportant part of the procedure, and may or may not be used, depending on the case. Without counterpressure the possibility of loss of vitreous is lessened.

Improper application of the technic may lead to trouble. The comment has been expressed by various operators that in use of the suction instrument which I advocate there is a tendency for the suction

cap to slip off the lens. This likelihood can be lessened by observance of two factors. 1 In rotating or sliding the lens, the suction cap must be kept parallel with the body of the lens. Any tendency to change the angle of rotation or the parallel alignment of the lens and cap may easily cause the disk to slip from the lens capsule. 2 The lens must not be withdrawn too rapidly. Time must be taken to break the zonular fibers properly. If the suction cap does slip off the lens, it is simply replaced, and nothing is to be feared if the procedure is under control. Slipping occurs when the lens is dislocated and partially delivered.

#### CONTRAINDICATIONS TO THE SUCTION TECHNIC

Use of the suction instrument is contraindicated in several types of cases. When the following conditions exist, other, established, procedures should be resorted to in removing the lens. (1) fluid vitreous, when due to high myopia or the result of a chronic inflammatory process in the eye, and (2) dislocated lens, of either traumatic or congenital origin.

Fluid vitreous may be suspected to exist, and its presence be determined, before operation. Unfortunately, however, one may not be aware of its presence until the corneal section is made and vitreous begins to seep out. Suction is not advocated in such cases, as further and more rapid loss of vitreous may follow. One of the other procedures, such as that advocated by Kirby,<sup>25</sup> is more likely to be followed by successful removal of the lens.

In the case of a dislocated lens, the so-called margin of safety is small to begin with, and the application of the suction instrument may be difficult unless the lens presents immediately in the wound. Otherwise, sufficient resistance to the instrument is not present, and either vitreous may be drawn up with the syringe or the lens may be further dislocated. I then turn to one of the accepted methods of extraction.

#### OPERATIVE TECHNIC

It should be emphasized that with the suction instrument either the sliding or the tumbling technic may be employed in delivering the lens. However, it has been found that it is much more satisfactory to tumble a lens with suction than to slide it out. The suction is more likely to be released from the capsule if the latter method is used. However, the sliding technic is indicated with the suction instrument when the lens is dislocated easily and presents itself in the wound.

With the tumbling technic, one must rotate the suction cap in an arc parallel to the vertical plane of the lens. This is necessary to

<sup>25</sup> Kirby, D. B. Intracapsular Cataract Extraction, *Am J Ophth* 25:269, 1942.

insure continued even pull on the lens. In the performance of this method, the hand and wrist must be lowered as the cap is rotated, or improper rotation will tend to raise one edge of the suction cup from the capsule of the lens.

The instrument advocated for the suction method of extraction is my modification of the Dimitry<sup>18</sup> suction instrument, illustrated in figure 3.<sup>26</sup> This apparatus consists of the Dimitry syringe modified to increase the suction, a 6 inch (15 cm)

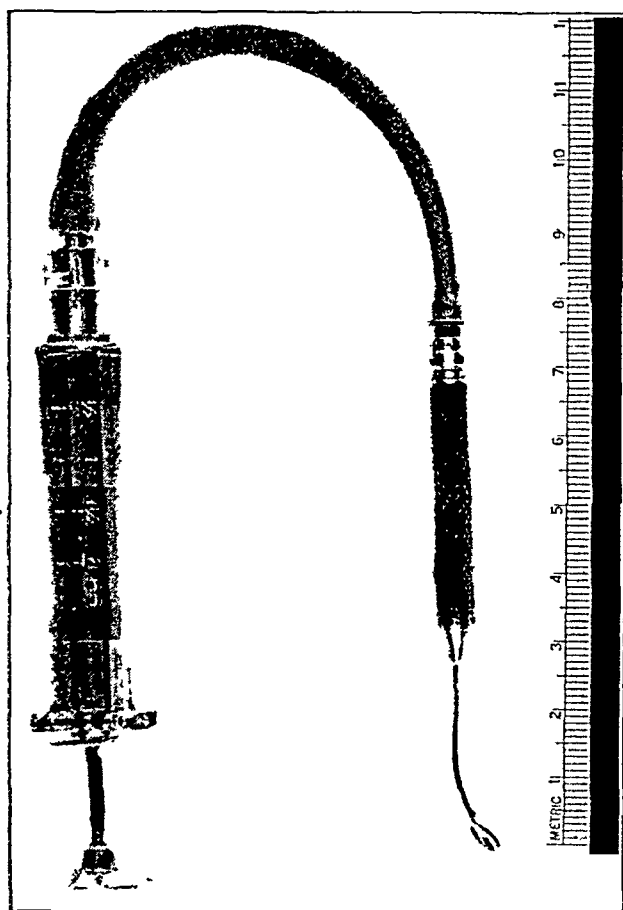


Fig 3—Suction instrument for cataract extraction devised by Thomas<sup>26</sup>

length of firm rubber tubing and a special adapter with a convenient handle for manipulation of the suction cup. This instrument displaces a 5 mm column of water 65 mm., an increase of 20 mm. over the original drawing power. The advantages of this instrument are its easy manipulation, adequate suction power and the self-controlled suction, which is automatically cut off when the cup is removed from the lens. The cup is inserted into the chamber and placed flat on

<sup>26</sup> Thomas, C I Suction Instrument for Cataract Extraction, *Am J Ophth* 28 317, 1945

the lens capsule. Slight counterpressure just below the limbus often helps the operator in securing a firm grasp on the capsule. The assistant then applies the suction. The process of delivery is then carried out either by sliding or by tumbling the lens. Unless the lens presents itself in the wound and is easily dislocated, it has been found that tumbling enables the suction to be held more firmly than the sliding method. It should be emphasized that reapplication of the suction cup is not a hazard, and I have done this often with no complication in delivering the lens. An alert assistant enables immediate reapplication of suction to be carried out.

Motor-produced suction often has greater drawing power, but is not an essential and calls for the use of needless machinery. The greatest danger in this method is that it requires extra manual control to cut off the suction, since suction is not self controlled, as in the syringe. In motor suction, unless the cup is squarely on the lens, the suction may be disastrously applied. This untoward occurrence is easy when one is working at the lower periphery of the lens. How-

TABLE 1—*Data on 618 Attempted Intracapsular Extractions*

		Loss of Vitreous
Successful forceps extraction	450	25
Successful suction extraction	75	
Ruptured capsule with forceps	87	
Ruptured capsule with suction		
Zonule too resistant and capsule purposely ruptured	6	
Total	618	

ever, the complication will not be encountered with the syringe, as the control of its drawing power depends on the proximity of the cup to the capsule itself.

Barraquer<sup>17</sup> made a point of subluxating the lens by rotation. This maneuver is an excellent one, but is not necessary in every case. If the zonular fibers are found to be especially elastic, either this maneuver can be tried or counterpressure can be exerted below and near the limbus to break these fibers. Rotation may not be necessary if the lens is dislocated readily.

## COMMENT

In 75 of the 618 cases of intracapsular extraction of the lens studied, it was decided at operation to use the suction method. The character of the lens and the tunicity of the capsule were necessarily studied before the method to be used was decided on.

Table 1 shows the relative frequency of rupture of the capsule when the lens forceps is used, as compared with the incidence of rupture with the use of the suction instrument. The lens capsule forceps used were the Arruga, the Kirby and the Verhoeff type. It was found that

when the lens capsule ruptured it did so in almost any stage of the delivery, but most frequently before the lens had become completely dislocated. If the zonular fibers were found to be more resistant along either the nasal or the temporal side, and if one of these sites was the last to be dislocated, rather than continue the traction on the lens, one could "roll out" the lens on the side toward the resistant fibers, thereby lessening the chances of rupturing the capsule. Rupture of the capsule indicated that one of the following conditions existed: (1) The zonular fibers were more resistant than the capsule, (2) there were adhesions around the lens itself, holding it in the fossa, or (3) the area of traction was distributed over too small an area to bear the weight of the lens itself. The last factor was believed to be a frequent cause of failure in delivering the lens in the capsule, and its importance is apparent when one studies the traction lines shown in figure 2. In table 1, there is a conspicuous absence of cases in which the capsule was ruptured when the suction instrument was used. The percentage

TABLE 2—*Conditions in Which The Suction Method Is Indicated*

Swollen, hypermature lens	30
Capsule too tight for application of forceps	28
Friable capsule	15
Exfoliation of lens capsule	2
Total	75

of cases in which vitreous was lost also bears comment. In all such cases of loss of vitreous the most likely cause was counterpressure. It should be kept in mind that this may not be a factor in extraction by suction.

Table 2 shows the types of cases in which the suction method is used to the greatest advantage. Again I wish to emphasize that the operator should not decide on the type of operation to carry out before the chamber is opened and the lens examined. If any of the four conditions shown in table 2 exist one should immediately proceed with extraction by suction. Cases with exfoliation of the lens capsule are included in this group, as with this condition intracapsular extraction is considered the safest method and the surest way by which to carry out the extraction is with the suction instrument.

#### CONCLUSIONS AND SUMMARY

The method used for any cataract extraction should vary with the judgment of the surgeon.

The suction method of cataract extraction is used to its greatest advantage in cases in which the (1) lens is hypermature (2) the cap-

sule is tense, (3) the capsule has exfoliated, (4) the lens must be dislocated before it is tumbled or slid out of the fossa, (5) the capsule is friable and will not stand any tension

The advantages of the suction technic are (1) more even distribution of traction and (2) less counterpressure

Pitfalls of the operation are discussed

Contraindications to the use of the suction method are indicated

An analysis of 618 cases of intracapsular extraction is presented to show the comparative frequencies of rupture of the capsule with use of the lens forceps and with the suction instrument

10515 Carnegie Avenue

# Clinical Notes

## DISPENSER FOR ADHESIVE TAPE

MORGAN B RAIFORD, M D \*  
PHILADELPHIA

In carrying out routine hospital dressings in ophthalmic cases, there are few occasions which necessitate various lengths of adhesive tape. Cutting individual pieces of adhesive tape one at a time is a slow process, and they are not always of equal lengths. A dispenser was designed which enables the ophthalmic nurse to have ready for dressings strips of adhesive tape of similar lengths. This dispenser is made of plastic material and is 15 cm wide and 60 cm long.

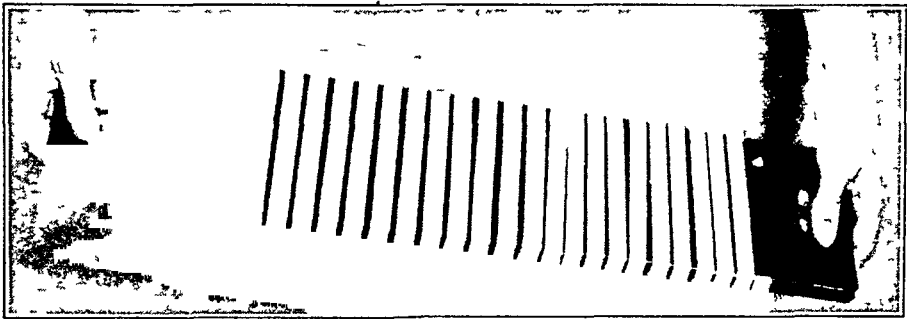


Fig 1—Side view of the adhesive tape dispenser with tape applied

Two fingerholes, one at each end, enable the nurse to hold the dispenser easily either in the application or in the removal of the adhesive tape. Two small grooves run the entire length of the edge of the dispenser, allowing the bandage scissors to cut the tape easily. Small free tips of adhesive tape overlapping the grooved edges facilitate grasping it for removal. The adhesive tape does not lose any of its adherent qualities by contact with the plastic surface. This dispenser has been very satisfactory not only as a convenient and efficient carrier for adhesive tape, but as a time saver in ophthalmic nursing.

The dispenser was made by the John L. Van Arkel Company, Haddonfield, N. J.

Nineteenth and Lombard Streets

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\* Resident, Department of Ophthalmology, Service of Dr. Edmund B. Spaeth, Graduate Hospital of the University of Pennsylvania

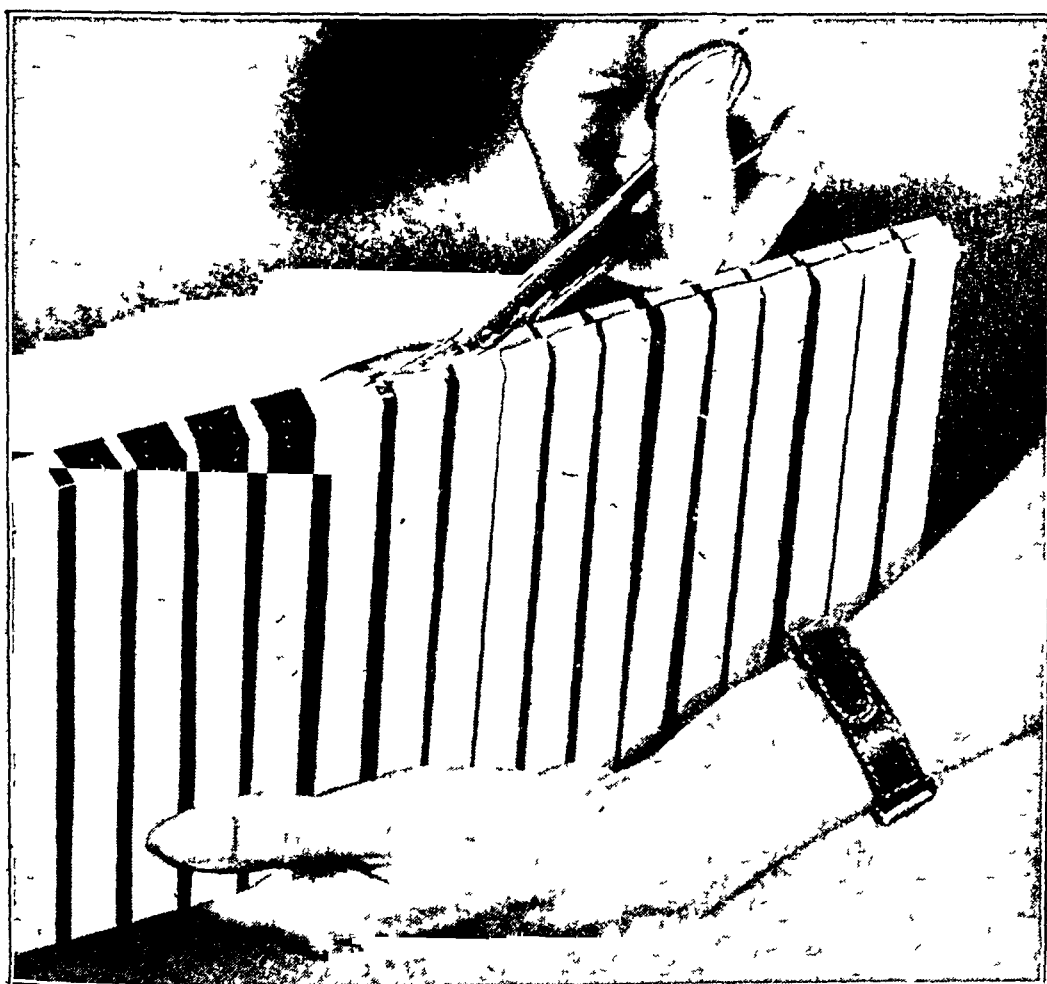


Fig 2—Cutting the adhesive tape with bandage scissors



## Correspondence

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### USE OF GLASS IRRIGATOR FOR ANTERIOR CHAMBER

*To the Editor* —I still feel justified in using my blue-tipped glass irrigator, in spite of the fact that an accident has been reported in which a tip of the irrigator broke and remained in the anterior chamber

I wish first to explain the function of my irrigator as it is designed. The blue tip certainly needs no explanation. The bulbous part of the irrigator serves two purposes. First, it prevents too forcible irrigation of the anterior chamber, for no matter how hard the rubber bulb is pressed there is a steady stream of fluid under uniform pressure. Second, the enlargement serves to prevent the introduction of minute particles of rubber into the eye which often come from the inside of the rubber bulb. These particles always present themselves in the small bowl before they can be introduced into the eye. I have seen 3 cases of particles of rubber in the anterior chamber. In 1 case definite harm was done, and in the others the position of the particles was confined to the anterior chamber, owing to the fact that there was a fine secondary membrane. The eyes showed no irritation due to the presence of these foreign bodies.

Probably a few words would be in order to explain how to irrigate the anterior chamber in the most efficient manner. In the first place, the irrigator for the anterior chamber which was made according to my specifications was never intended to be used as a spatula, either for the iris or for the wound, although on numerous occasions I have seen this maneuver performed. Ocular instruments are instruments of precision, and I do not think it possible to replace a well made spatula with an irrigator for the anterior chamber. As they serve distinctly different purposes, their construction must vary accordingly.

The following procedure, I think, is safe. Before the irrigator is to be used, I take a pledget of sterile cotton and wipe the irrigating tip from the under side. This accomplishes a number of purposes. If the tip is jagged, the defect can readily be seen by the contrast between the blue and the white. If it is cracked, the slight pressure exerted in this manner will readily indicate whether or not the instrument is safe to use.

In the actual irrigation, the irrigator can be moved from side to side, provided the operator's hand is not a fist. The irrigation should be started before the point of the irrigator is introduced into the wound, and it should also be borne in mind that it is often possible to wash out the anterior chamber successfully without introducing even the tip of the irrigator into the wound if the eye and the irrigating stream are in proper coaptation. For one not skilled in this operation, it is safer to irrigate from either angle of the wound, so that if the patient suddenly looks up the point of the apparatus will slip out of the wound and there will be no folding of the cornea.

Probably the most important part of the whole procedure is the direction of the stream of the irrigating solution. I have watched

many surgeons irrigate the anterior chamber, and some of them do not seem to realize that the proper way to remove material from the chamber is to direct the stream against the posterior surface of the cornea, not into the vitreous, and not at the material which is to be removed

I am still of the opinion that, if used with caution, my irrigator is the best available though not perfect

WILLIAM BROWN DOHERTY, M D , New York

150 West Fifty-Fifth Street

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#### CLOSURE OF CENTRAL RETINAL ARTERY AFTER GENERAL ANESTHESIA

*To the Editor* —If any ophthalmologist has had occasion to see a case of closure of the central retinal artery, first recognized shortly after the patient came out of a general anesthesia, will he be so kind as to convey the details to me? Please note which eye was affected, type of anesthesia used, length of operation and its nature, whether or not the patient went into shock at the time of the operation and whether there was any evidence, such as corneal abrasion or ecchymosis of the lids, that the eye had been pressed on during the anesthesia

I GIVNER, M D , New York

108 East Sixty-Sixth Street (21)

## News and Notes

EDITED BY DR W L BENEDICT

### GENERAL NEWS

**Foundation for Vision Terry Center for Visually Handicapped Children**—The Foundation for Vision is the philanthropic organization which has carried on the projects of the late Dr Theodore L Terry. His investigation of retrolental fibroplasia has been continued at the Massachusetts Eye and Ear Infirmary by Dr Everett Kinsey, the clinical studies have been made by Dr Merrill F King. A training course for the mothers of children afflicted with this type of blindness was arranged and given by Dr Terry to a large group of mothers and children at the Perkins Institution, in Boston. Since his death, a few mothers have been instructed from time to time, but no organized work has been carried on. This course is to be reopened next summer at the Perkins Institute under the auspices of the Foundation, as the Terry Center for Visually Handicapped Children. The details can be obtained from Dr Gabriel Farrell, of the Perkins Institute, when arrangements are completed.

**Ophthalmological Study Council**—The course in the basic subjects of ophthalmology will be given next summer, using the facilities of Westbrook Junior College in Portland, Maine. This is the fifth session of this course, which is under the supervision of the Ophthalmological Study Council, sponsored by the Foundation. Dr Walter B Lancaster, who organized and developed the previous courses, asked to be relieved of responsibility at the meeting of the Foundation in June and will be succeeded as director by Dr Parker Heath, clinical professor of graduate ophthalmology at the Harvard Medical School. The arrangements for this course will be essentially the same as those for the previous sessions. The dates of the course will be published in the journals as soon as a decision has been reached.

**American Board of Ophthalmology**—Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a written qualifying test. These tests are held annually in various parts of the United States.

Registration is already closed for the next test, to be given in January 1949.

Applications are now being accepted for the 1950 written test. They will be considered in order of receipt until the quota is filled.

The practical examinations for acceptable candidates in 1949 will be held as follows: San Francisco, March 21 to 24, New York, June 11 to 15, St. Louis, October 15 to 19, and Boston, in December.

A supplementary list of diplomates from January 1948 to January 1949 will be sent without charge to all purchasers of the Board's "Directory." This supplementary material is arranged alphabetically and geographically. No biographic material is included.

Diplomates are urged to keep the office of the Board informed of all changes of address.

The officers for 1949 are chairman, Dr Frederick C Cordes, vice chairman, Dr John H Dunnington, secretary-treasurer, Dr S Judd Beach, and assistant secretary, Dr Edwin B Dunphy

Communications should be addressed to the Executive Office, American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine

**German Ophthalmological Society.**—The first meeting of the German Ophthalmological Society since 1938 has just been held in Heidelberg. As the hotels were occupied by the military personnel, the doctors were lodged in hospitals and in student barracks. The meetings were held in the University, under the direction of Professor Engelking, and lasted three days, the session beginning at 8 o'clock in the morning and continuing, with two hours' intermission, until 6 o'clock. A general dinner for participants took place on the first and second evenings, the food was good, as a German colleague in Montevideo had made a gift of butter, sugar, coffee and tobacco. The scientific standard of the meeting was high, many good papers were presented and will be worth careful study when the *Transactions* appear. Among the foreign guests were J D Noidenson, of Stockholm, and D G Cogan, of Boston. Dr Cogan gave the opening address.

The meetings were a proof of the wonderful way in which the German ophthalmologists are overcoming their great difficulties. Arrangements were discussed for the proper celebration of the Helmholtz centenary. The new president is Prof K Wessely, of Munich.

**Estelle Doheny Eye Foundation Lecture in Ophthalmology.**—Dr Cecil S O'Brien, professor of ophthalmology at the State University of Iowa College of Medicine, will deliver the Estelle Eye Foundation Lecture at the Los Angeles County Medical Association Building in Los Angeles on Nov 8, 1948. His subject will be "The Surgical Treatment of Strabismus". The first of these annual lectures presented by the Estelle Doheny Eye Foundation in Los Angeles was delivered by Dr Alan C Woods, professor of ophthalmology at Johns Hopkins University and director of the Wilmer Ophthalmological Institute, on Dec 17, 1947.

**Seminar in Ophthalmology and Otolaryngology, University of Florida.**—The Graduate School of Medicine of the University of Florida will hold a midwinter seminar in ophthalmology and otolaryngology at Miami Beach, Jan 10 to 15, 1949. The lecturers in ophthalmology will be Dr John H Dunnington, New York, Dr Avery Prangen, Rochester, Minn, Dr Georgiana Theobald, Chicago, Dr Derrick Vail, Chicago, and Dr Alan C Woods, Baltimore.

Early registration is advisable. The registration fee is \$40. Application may be made to Dr Walter T Hotchkiss, 541 Lincoln Road, Miami Beach, Fla.

**Annual deSchweinitz Lecture.**—The eleventh annual deSchweinitz lecture, sponsored by the College of Physicians of Philadelphia, Section on Ophthalmology, will be delivered by Dr William L Benedict on November 18 on "Surgical Treatment of Tumors and Cysts of the Orbit."

## UNIVERSITY NEWS

**Refresher Course in Ophthalmology and Otolaryngology**—The University of Toronto Faculty of Medicine announces a refresher course in the combined subjects of practical ophthalmology and otolaryngology, to be given from Jan 24 to Jan 29, 1949

The course will be so arranged that the operative procedures and bedside conferences of the one specialty will be held in the mornings and the didactic conferences or lectures in the afternoons. The reverse of this procedure in the other specialty will make it possible for each applicant to pick whatever subjects may be of interest to him.

Guest speakers will give lectures and clinics in both subjects of the course. The fee will be \$60. The course will be given for a minimum of 10 students and a maximum of 20 students. Application should be made to the Medical Office, University of Toronto, and the closing date for application will be Nov 30, 1948.

## SOCIETY NEWS

**Two New Ophthalmologic Societies in Rumania**—Notice has been received of the formation of two new ophthalmologic societies in Rumania. The first will be known as the Rumanian Society of Ophthalmology in Timisoara, president, Dr Nicolas Blatt, and secretary, Dr Nicolas Zolog. The second is the Rumanian Society for the Prevention of Blindness, president, Dr Nicolas Blatt, and secretary, Dr Virgil Popovici.

## PERSONAL NEWS

**Dr Roscoe J Kennedy Appointed Head of Department of Ophthalmology of the Cleveland Clinic**—Dr Roscoe J Kennedy has been appointed head of the department of ophthalmology at the Cleveland Clinic. After receiving his medical degree in 1931 at the State University of Iowa College of Medicine, Dr Kennedy interned at the Harper Hospital, at Detroit, and served as resident at the Buffalo General Hospital and at the Wills Hospital, Philadelphia.

Dr Kennedy came to the Cleveland Clinic in 1937 to complete a fellowship course of study and was appointed to the professional staff in 1938. In World War II he served for four years with the medical corps of the United States Navy in the Southwest Pacific, holding the rank of captain.

Dr Kennedy was certified by the American Board of Ophthalmology in 1939 and has made various contributions to medical journals. He is secretary-treasurer of the Cleveland Ophthalmological Club and is also a member of the Cleveland Academy of Medicine, the American Medical Association and the American Academy of Ophthalmology and Oto-Laryngology. He was born at New Hampton, Iowa, and attended Notre Dame University.

**The Eightieth Birthday Celebration of Sir John Herbert Parsons**—The September issue of the *British Journal of Ophthalmology* is a special number dedicated to Sir John Herbert Parsons on the occasion of his eightieth birthday. The number contains twenty-three articles, by friends from many countries, and three introductory expressions of appreciation, by Prof E D Adrian, Prof J van der Hoeve and R R James. The members of the Faculty of Ophthalmology and the Ophthalmological

Society of the United Kingdom presented Sir John Herbert Parsons with a portrait in oil, painted by John Gorlay, in honor of his eightieth birthday. The presentation took place at the Royal College of Surgeons on Sept. 3, 1948. The presentation speech was made by Sir Stewart Duke-Elder, the portrait was then unveiled by Lady Duke-Elder, and Sir John made a brief reply.

**Dr. Arthur J. Bedell Lectures at Meeting of Pan-Pacific Surgical Association.**—Dr. Arthur J. Bedell, of 344 State Street, Albany, N. Y., attended the meeting of the Pan-Pacific Surgical Association in Honolulu, Hawaii, August 30 to September 13. He gave a series of three lectures before the society.

# Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

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## Congenital Anomalies

OPHTHALMOLOGIC IMPORTANCE OF ANOMALIES OF THE SELLA TURCICA  
R BAROLOZZI, Arch Soc oftal hispano-am 7. 671 (July) 1947

While making anatomic studies of a number of skulls, the author observed an anomaly of the sella turcica which may have a bearing on the syndrome of glaucoma without hypertension. This anomaly consisted of fusion of the anterior, middle and posterior clinoid processes by means of a bony bridge. This observation is not new, but no importance has been attached to it. It is not necessarily a process of old age. The fusion of the anterior and the middle clinoid process gives rise to the formation of a circular orifice (the carotid foramen), through which the terminal portion of the internal carotid artery passes. The anomaly has nothing to do with displacement of the optic nerve. It could, however, influence the course of the internal carotid artery, which in passing through the anomalous carotid foramen could be pushed against the optic nerve, forming a closer than normal contact.

This anomaly would have practical interest, since it could explain cases of atrophy of the optic nerve and chiasmic lesions in which no calcification of the vessel is apparent.

H F CARRASQUILLO

## Cornea and Sclera

THE PRESERVATION OF CORNEAL TISSUE BY FREEZING AND DEHYDRATION  
H M KATZIN, Am J Ophth 30: 1128 (Sept) 1947

Katzin attempted to preserve rabbit corneas for transplantation by rapid freezing at the temperature of liquid nitrogen and dehydrating *in vacuo* at  $-40^{\circ}\text{C}$ . These grafts took and healed in place but did not remain clear, despite various modifications in technique.

W S REESE

LOCAL SULPHONAMIDE THERAPY OF DENDRITIC ULCER  
H L HUGHES, Brit J Ophth 32: 43 (Jan) 1948

A series of 16 cases of dendritic ulcer of the cornea treated locally with sulfonamide compounds is presented. The mode of treatment was to instil 6 per cent "albacid" (azosulfamide) ointment three times a day and paint the entire corneal surface once daily with 30 per cent solution of azosulfamide.

As Sorsby pointed out, the good results obtained with sulfonamide therapy raise the question whether dendritic ulcer is to be regarded as a herpetic virus infection. It is possible that the high concentration reached with local treatment is effective against the virus.

W ZENTMAYER

CORNEAL DYSTROPHY ASSOCIATED WITH IRITIS AND ARTHRITIS G H. B BLACK, Clin Rep Adelaide Childrens Hosp 1:70 (Nov) 1947.

Black reports a case of a band-shaped area of corneal dystrophy and iritis affecting both eyes in a child aged 10 years. Definite bony changes were present in the proximal phalanx of the thumb, and there was sub-acute arthritis of the left knee joint.

W ZENTMAYER.

TREATMENT OF THE SERPIGINOUS ULCER WITH PENICILLIN P MATA, Arch Soc oftal hispano-am 7:641 (July) 1947

The author treated 30 patients with serpiginous ulcer of the cornea with penicillin. To the conclusions given by Keefer in 1943 on the findings of the Committee on Chemotherapeutic Agents, based on the reports of more than twenty groups of investigators which made their studies in the United States, Mata adds that the local application of penicillin as used in treatment of serpiginous ulcer has the great advantages of acting directly on the infectious agents, that its antibiotic action is not influenced by the presence of blood, pus, exudates or autolytic products and that it must be administered periodically and continuously, using the maximum concentrations if necessary without fear of any deleterious effect on the tissues.

In reporting the results obtained with the treatment, he divided his series of cases in four groups: (1) 3 cases, in which treatment began with sulfonamide drugs, with no improvement, followed by administration of penicillin; (2) 9 cases of moderately severe lesions; (3) 9 cases of severe lesions; and (4) 9 cases of advanced lesions with complications. In groups 1, 2 and 3 the results of treatment with respect to cure were excellent. In group 4, in spite of the advanced stage of the ulcers and the existing complications, the results were satisfactory.

The penicillin used was of the purest quality. It was administered by iontophoresis, using a Wertz electrode and solutions of high concentration (from 2,500 to 6,000 units per cubic centimeter), by subconjunctival injections of maximum doses of 5,000 units and by continuous instillations of solutions of up to 10,000 units per cubic centimeter.

Ascorbic acid was also given intravenously in many of the cases.

H F CARRASQUILLO

### General Diseases

LYMPHOGRANULOMA VENEREUM H G SCHEIE, A S CRANDALL and W HENIE, J A M A 135:333 (Oct 11) 1947

In the 5 cases described the corneal lesions were identical. In the 1 case in which the lesion was followed from its onset, the condition began as ordinary keratoconjunctivitis localized to the upper portion of the limbus. Corneal infiltrates appeared within the upper limbus, and as they increased in number they became confluent, forming an arc involving one-third to one-half the circumference of the cornea. The entire thickness of the cornea became involved, but the process gradually became superficial centrally over its advancing border. A dense superficial vascularization from the limbus covered the infiltrate so profusely that it elevated the surface like an epaulet. A milky iridocyclitis was present.



Evidence supporting the diagnosis of lymphogranuloma venereum consisted in the following observations (a) a positive Frei reaction in all cases, (b) involvement of inguinal lymph nodes, active in 1 case and healed in 3 cases, (c) a strongly positive complement fixation reaction in 1 case, and (d) in the corneal lesion of the same case, inclusion bodies compatible with lymphogranuloma venereum as shown by biopsy. Although the prognosis is serious, sulfathiazole or sulfadiazine should be given in full therapeutic doses for not less than three weeks.

W ZENTMAYER

"MAPHARSEN" IN REITER'S DISEASE E N KHOURY, *J Urol* 58:221 (Oct) 1947

Khoury points out that Reiter's syndrome has a basic triad of non-gonococcal urethritis, conjunctivitis and arthritis. The general belief is that it is one of the many virus infections. In cases reported in the literature, the course was generally protracted, but this is not an invariable observation, inasmuch as in at least 1 of the 2 cases reported here the disease was benign and cleared in a comparatively short time. In the second case the condition may be classed as moderately severe. However, it did cause protracted disability. Large doses of oxophenarsine hydrochloride U S P ("mapharsen"), which were started four months after onset of the urethritis, caused such a rapid and dramatic response that the possibility of a coincidental spontaneous regression cannot be rationally entertained. The author thinks that in future cases of this syndrome this form of therapy should have a trial. "Mapharsen" was given in two injections a week for three weeks, then one injection a week for four weeks. The dose was 0.06 Gm, administered intravenously.

J A M A (W ZENTMAYER)

RETINAL COMPLICATIONS OF DIABETES MELLITUS J L R CANDELA, *Arch Soc oftal hispano-am* 7: 851 (Sept) 1947

Clinically, the presence of diabetic retinopathy cannot be attributed to the hyperglycemia of diabetes. It is a well established fact, however, that diabetic patients, more particularly those presenting retinal complications, have a high capillary fragility. The author, following the technic of Gothlin, found in these patients a moderately high petechial index. He also found in dogs with alloxanic diabetes disturbances in the plasma proteins with no relation to the lipids and cholesterol contents, as described by other observers, but coinciding with the presence of the retinal lesions of the disease.

Experimentally, the alterations in the plasma proteins are constant in the diabetes of pancreatic origin, and in 80 to 100 per cent of the cases of the alloxanic type.

Candela has prepared a pancreatic extract the administration of which would bring to normal the altered plasma proteins much sooner and more completely than the establishment of any type of diet. The retinal lesions present are also considerably improved. Besides this, by the use of the extract, the complementary activity of the plasma is restored to normal, and the elimination of nitrogen in the urine is also decreased.

H F CARRASQUILLO

## Glaucoma

CYCLODIALYSIS, MULTIPLE OR SINGLE, WITH AIR INJECTION O BARKAN, *Am J Ophth* 30:1063 (Sept) 1947

Barkan describes his method of cyclodialysis, multiple or single, combined with injection of air. The latter procedure is designed to control hemorrhage, widen the cyclodialysis cleft and make it visible and, by restoring and deepening the anterior chamber, make possible multiple cyclodialysis. The results reported are based on operations performed on 83 eyes.

W S. REESE

THE SIGNIFICANCE OF THE BASE PRESSURE IN PRIMARY GLAUCOMA A B REESE, *Am J Ophth* 31:25 (Jan) 1948

The importance of study of the base rather than the peak pressures in glaucoma, particularly the long range trend, is emphasized. Operative measures are based on these studies, together with the type of glaucoma.

In glaucomatous eyes the height to which the pressure rises is referred to as the "peak pressure," and the depth to which the pressure descends, as the "base pressure." Any sustained elevation of the base pressure indicates permanent damage to the filtration angle. The more advanced the glaucoma, the more nearly the base pressure approaches the peak pressure, so that in absolute glaucoma they tend to merge.

W ZENTMAYER

## Injuries

OBSERVATIONS ON 300 CONSECUTIVE CASES OF OCULAR WAR INJURIES J G BELLOWS, *Am J Ophth* 30:309 (March) 1947

The article does not lend itself well to abstracting. The cases are considered under (1) injuries caused by air blasts or burns, (2) concussion waves reaching the eye through the tissues, caused by direct impact on an adjacent structure or, less frequently, at a more distant point, and (3) direct impact of a missile on the eyeball.

W S REESE

OCULAR LESIONS FOLLOWING THE ATOMIC BOMBING OF HIROSHIMA AND NAGASAKI J J FLICK, *Am J Ophth* 31:137 (Feb) 1948

Flick states that the transient nature of the condition and the chronologically short period over which the studies were made do not permit definite conclusions. It seems safe, however, to conclude that the ocular lesions here described are directly related to the deficiency in blood elements, and in no way directly related to the action of radiant energy on the eye. The lesions were observed to disappear in persons recovering from the hematopoietic depression, with no residual damage to the eye. It is believed that this healing occurred in all patients who survived the irradiation and that no permanent residual damage resulted from the retinal lesions. As to the vexatious question of radiation damage to the lens, time alone will tell.

W S REESE

### Lens

MICROPUNCTURE OF HYPERMATURE CATARACTS WHOSE CAPSULES CANNOT BE GRASPED WITH THE CAPSULE FORCEPS J SEDAN and S SEDAN BAUBY, *Ophthalmologica* 114 65 (Aug) 1947

In a number of hypermature cataracts, it is impossible to grasp the capsule with the ordinary capsule forceps in performing an intracapsular extraction. The authors find that if a knife needle is inserted through the peripheral iridotomy wound into the lens, sufficient fluid lens material comes out of the puncture wound to enable one to grasp the lens capsule with the capsule forceps and extract the lens intracapsularly, in the usual manner. They also cite a somewhat similar variation of this procedure, described earlier by a colleague, Charles Thomas, of Nancy.

F H ADLER

IRIDODIALYSIS AFTER EXTRACTION OF CATARACT CURED BY ELECTROCOAGULATION DIATHERMY K SAFAR, *Ophthalmologica* 114 77 (Aug) 1947

In cataract extraction in which the iris has been torn from its roots, giving rise to iridodialysis, the root of the iris may be brought forward by means of a small hook or fine iris forceps through a small keratome incision at the limbus. It is pulled into the wound and fastened there by means of gentle electrocoagulation. This method is simple and effective, and the scar formed holds the iris in place. It may be employed with success in cases of aphakia, as well as in eyes with lenses in which the iridodialysis is traumatic.

F H ADLER

### Lids

CORRECTION OF SOME FORMS OF ACQUIRED PTOSIS EDMUND B SPAETH, *Plast & Reconstruct Surg* 2: 37, 1947

The types of blepharoptosis are classified, and recommendations are made as to the operation of choice for the individual type. The classification of congenital blepharoptosis is based mainly on whether the superior rectus muscle or the third and sixth nerves are involved. Acquired blepharoptosis is classified chiefly on a basis of nerve or tissue damage. Three types of surgical treatment are especially recommended: (1) use of bands for support, according to the method of Hess, (2) utilization of fibers of the orbicularis, as devised by Reese, and (3) resection of the levator muscle and the tarsus, employing the Blascovics technic.

LOREN P GUY

THE OCULOPALPEBRAL SYNDROME OF THE PREMENOPAUSE A KOUTSEFF, *Bull Soc d'opht de Paris*, November-December 1946, p 92

The author reports 2 observations in which he believes that the role of the pituitary gland may be of importance in the control of edema of the lids previous to menstruation. Estrogen is thought to be the element which is basically responsible for the syndrome.

L L MAYER

### Methods of Examination

FACTORS IN DIAGNOSIS OF ANISEIKONIA AND PAIRED MADDOX-ROD TESTS P W MILES, *Am J Ophth* 30:885 (July) 1947

Miles outlines his views on factors in the diagnosis of aniseikonia, tests for stereoscopic acuity and binocular methods of noncycloplegic refraction. He describes a method of measuring aniseikonia with paired Maddox rods.

W S REESE

ROENTGENOSCOPIC METHOD APPLICABLE TO THE DIAGNOSIS AND LOCALIZATION OF INTRAOCULAR FOREIGN BODIES M ESTEBAN, *Arch Soc oftal hispano-am* 7:1084 (Nov) 1947

By making use of x-ray appliances which have permitted the odontologist to make roentgenoscopic studies of the alveolar processes of the teeth, Esteban has succeeded in making fluoroscopic studies of the eye and determining the presence and localization of intraocular foreign bodies. He used for his observations a Ritter dental x-ray unit. The method of examination is fully described, and the advantages of the roentgenoscopic study over the examination of the film are enumerated.

H F CARRASQUILLO

PERIMETRIC LOCALIZATION OF LESIONS OF THE FUNDUS A VAZQUEZ BARRIERE, *Arq brasil de oftal* 10:1, 1947

By ophthalmoscopic localization is implied the determination of the situation of lesions in the fundus with relation to fixed points of reference, such as the disk, in the internal part of the eye, and the sclero-corneal limbus or the optic nerve, in the external part. The procedures for localization of retinal tears can be divided into two groups: (a) those carried out before operation, and (b) those carried out during the operation. Only the first group is considered. A historical summary of the methods of localization is presented. The author has made several modifications in the technic, and these are presented in great detail.

M E ALVARO

### Neurology

COMPLETE REMOVAL OF CRANIOPHARYNGIOMA WITH RECOVERY FROM BLINDNESS W T GRANT, *Bull Los Angeles Neurol Soc* 12:53 (March) 1947

Grant was unable to find the report of a case of total removal of a suprasellar cyst or craniopharyngioma. He presents such a case. A boy aged 2 years was apparently well until he fell on his forehead. Failing vision began in four days, and the boy was totally blind in twelve days. At operation, four weeks and two days after the onset of blindness, a large suprasellar cystic tumor was collapsed by aspiration and removed intact. It was necessary to divide the right optic nerve to accomplish this. A narrow stalk connected the base of the tumor with the pituitary fossa. Response of the left pupil to light was present two days after operation, and the patient was able to see on the seventh day. He had useful vision at the time of the report. The history

suggested strongly that trauma was a factor in causing blindness. Cushing observed that the history of preceding trauma was surprisingly common as an apparent factor in stirring suprasellar cysts into activity. The absence of blood pigment in the wall of the cyst and of red blood cells in the cyst fluid would be against the contention that an intracystic hemorrhage had occurred at the time of the blow on the head. When the patient fell on the right side of his forehead, one would expect that the tumor would be thrust forward temporarily at the moment of the impact. This could hardly damage the optic nerves without causing visual impairment at once. But it could tear arachnoidal or other bands of tissue that were constricting the tumor. This would allow the lesion to expand gradually after the injury and would seem to fit the train of events in the present case.

W ZENTMAYER

HYSTERICAL AMAUROSIS EDSON PINHO, *Arq brasil de oftal* 10:16, 1947

The case is presented of a 19 year old girl who became suddenly blind in the right eye and had vision limited to counting fingers at 1 meter in the left eye. The globe and adnexa were normal. The personal history was one of shock after the imprisonment of her husband. Psychiatric treatment was carried out, mock operations being performed by her ophthalmologist, who explained the "treatment" in detail, but results were poor. Four months later she was examined again. Visual acuity was 1/10 at 5 meters in each eye. With her husband's return home, her vision became normal.

M E ALVARO

CLINICAL PICTURE OF RETROBULBAR NEURITIS IN CASES OF INTRACRANIAL TUMORS S LARSSON and B NORD, *Nord med (Hygiea)* 34:1059-1066 (May 2) 1947

Larsson and Nord warn that in cases of tumor in the anterior or middle fossa reduced vision and central scotoma, with or without papilledema or atrophy of the optic nerve, constitute an early symptom, the diagnostic value of which is frequently not recognized. The symptom is often attributed to sclerosis disseminata, and surgical intervention is thus delayed. Especially in cases with a protracted course, encephalographic studies are indicated. Eight personal cases, namely, 2 cases of meningioma of the olfactory groove, 2 cases of suprasellar meningioma, 1 case of meningioma originating in the lesser wing of the sphenoid, 1 case of adenoma of the hypophysis, 1 case of tumor of the hypophysial duct and 1 case of subfrontal meningioma, are described in detail. Diagnostic difficulties were presented in all, and retrobulbar neuritis was always prominent. Spontaneous improvement in vision suggested the erroneous diagnosis of sclerosis disseminata in the first 4 cases. In 1 case the ocular symptoms were ascribed to anemia, in 1, to possible cerebral trauma, in 1, to arteriosclerosis, and in only 1 case was the diagnosis of cerebral tumor made without preceding misconception.

J A M A (W ZENTMAYER)

## Ocular Muscles

EFFECTS OF PRACTICE AND THE CONSISTENCY OF REPEATED MEASUREMENTS OF ACCOMMODATION AND VERGENCE J BROZEK, E SIMONSON, W J BUSHARD and J H PETERSON, *Am J Ophth* 31:191 (Feb) 1948

Brozek, Simonson, Bushard and Peterson summarize their findings as follows

1 Measurements of ocular accommodation and vergence were made on 6 subjects under standard conditions

2 The measurements were repeated at intervals of two to three days in a series of eighteen testing sessions

3 Two preliminary trials were sufficient in the majority of the routine ophthalmic tests used to stabilize the scores at a plateau

4 The measurements provide reasonably constant characteristics of the individual subjects

W S REESE

PARALYSIS OF DIVERGENCE A U ZAVALA JR, *Arch Soc oftal hispano-am* 7:890 (Sept) 1947

The author discusses fully the controversial question of the existence of a separate innervation for the act of divergence. Supporting the view that such innervation is present, he makes the following statements.

(1) It is hard to believe that of the fusional movements only convergence should lack an antagonistic action, (2) the divergence movements not only are necessary to bring the visual axes from the position of convergence to that of parallelism, but also must be present to overcome an esophoria, (3) the tests used to determine the fusional movements show the presence of active movements of divergence, (4) it is erroneous to think that the limit of divergence corresponds to the position of rest brought about by complete relaxation of the convergence

A typical case of paralysis of convergence usually has the following characteristics (1) Onset is sudden and there is constant homonymous diplopia for objects farther than 25 or 50 cm, (2) the angle of deviation is usually small and at times unnoticeable, does not change when the eyes are directed laterally but does change when the eyes are moved up and down, (3) the field of fixation is normal, (4) base-out prisms will give to the patient normal binocular vision, (5) the angle of deviation is constant

The author describes his personal observation of a case

H F CARRASQUILLO

## Operations

SURGICAL TECHNIC IN OBTAINING FINE SCARS C R STRAATSMAN, *Plast & Reconstruct Surg* 2:21, 1947

Six long-established principles for good union of tissue with a minimum of scar formation are reiterated 1 A right angle incision is used, a bevel is avoided 2 Tension lines or natural folds are followed. 3 Relaxation of the edges is insured, avoidance of tension is essential. 4 Fine external sutures are used Silk sutures are generally preferred.

5 Skin sutures are removed early 6 Skin edges are supported This is done by use of adhesive bands or strips of collodion for at least four weeks after operation

Keloids present a problem Radium and roentgen therapy are helpful in prevention and removal Excision to within  $\frac{1}{8}$  inch (3 mm) of the external border of the keloid with suture of the edges together except where there is unavoidable tension is the surgical method of removal

LOREN P GUY

### Pharmacology

DISTRIBUTION OF PENICILLIN IN THE EYE AFTER SUBCONJUNCTIVAL INJECTION A SORSBY and J UNGAR, Brit J Ophth 51:517 (Sept) 1947

Sorsby and Ungar found experimentally that substantial concentrations of penicillin in the ocular tissues, many times the usual therapeutic level, can be obtained by the subconjunctival injection of crystalline penicillin in a dose of 50,000 units Adequate levels persist for six hours The concentrations are distinctly higher if epinephrine hydrochloride\* (1:1,000) is used as the solvent for the penicillin Observations on 5 human eyes support the results obtained experimentally

W ZENTMAYER

INFLUENCE OF COFFEE ON THE NORMAL OCULAR TENSION CYRO DE REZENDE, Arch de oftal de Buenos Aires 23:45 (Jan-March) 1947

After discussing modern knowledge of the chemical composition, pharmacodynamic action and effects which coffee exerts on the organism, the author reviews the studies which deal with the effect of coffee on ocular tonus

In this preliminary study, he presents the results of normal ocular tension under the effect of a coffee infusion with a concentration of 100 grains (16.5 Gm) of powder in 150 Gm of water

The results obtained on 100 subjects were as follows an increase in 43.5 per cent, a decrease in 27 per cent and no change in 29 per cent

M E ALVARO

### Physiology

DURATION OF BRIGHTNESS OF POSITIVE AFTER-IMAGES M PANNEVIS, Ophthalmologica 113:280 (May) 1947

An intensive after-image is projected onto a screen, the brightness of which can be varied and registered The brightness of the after-image is characterized by the intensity of the illumination of the screen which gives the same sensation of light as the after-image which is projected onto it (change from positive to negative after-image) The decrease in brightness follows the potential equation  $H = t^a e^b$ , in which  $a$ ,  $b$  and  $e$  are constants and  $t$  stands for time These processes are slower than the initial physical processes and, as far as can be judged, are different from and quicker than the higher nervous reactions In this case, each successive reaction of this series takes place at a slower rate than the preceding one Peripheral after-images, following the same light stimulus, are less intensive and fade out quicker In the area

of a central scotoma, the after-image can be entirely absent. On the return of vision, it appears first peripherally and then centrally.

F H ADLER

### Refraction and Accommodation

CONTACT LENSES I MANN, *Brit J Ophth* 31:565 (Sept) 1947

This paper is the presidential address delivered before the Contact Lens Society.

The problems of the contact lens fall under two types: those of optics and those of haptics. Much remains to be done if an optical accuracy comparable to that obtained with spectacle lenses is to be attained. The problem of the introduction of prisms, cylinders and bifocal glasses into contact lenses has still to be mastered. The author's interest in the subject is purely clinical. In a follow-up study of 100 patients, some of the problems have been formulated. Of the 100 patients, 61 were myopic, of these, 11 only wore a correction of — 5.00 D sph or under, the rest having very high corrections, up to — 22.00 D. Eleven had conical corneas, and the rest presented various disabilities, including high hypermetropia, binocular aphakia, corneal scars and dystrophies. The patients wore a single lens only for monocular aphakia. Of 84 patients who replied to the question whether they inserted their lenses dry or used a solution, 49 stated that they inserted them dry. Eight could not wear a lens at all. One, with sixteen to eighteen hours of wear every day, always put his lens in his mouth before inserting it, others used a boric acid solution, tap water or distilled water, with varying periods of tolerance. Various reasons were given for intolerance. For many, the corneal veil caused the most trouble. Other interesting data are given in the article.

W ZENTMAYER

### Retina and Optic Nerve

DICUMAROL AND RUTIN IN RETINAL VASCULAR DISORDERS A L MACLEAN and C E BRAMBEL, *Am J Ophth* 30:1093 (Sept) 1947

MacLean and Brambel conclude that sufficiently significant results have been obtained to warrant further clinical evaluation of dicumarol and rutin. They found dicumarol efficacious in treatment of occlusion of the central and tributary retinal arteries and of diabetic, degenerative and central serous retinopathies. Rutin was of benefit in cases of recurrent retinal and vitreous hemorrhage.

W S REESE

RETINAL ARTERY OCCLUSION I C MICHAELSON, *Brit J Ophth* 33:111 (Feb) 1948

A woman aged 41 had had defective vision in the left eye for six days. Vision was limited to counting fingers at 1 meter. Ophthalmoscopic examination showed occlusion of the macular branch of the inferior temporal artery. Fifteen minutes after the retrobulbar injection of acetylcholine there was notable diminution of the retinal opacity, which was confined almost entirely to the area between the affected artery and the macular vein, further clearing occurred, so that seven days later a faint sheathing was first noticed at the site of the spasm. Vision



improved to 6/24, the lower part of the letters being seen. The upper half of the field was lost to 2 mm white test objects at 1,000 mm.

W. ZENTMAYER

# TREATMENT OF RETINAL DETACHMENT. H. ARRUGA. Arch. Soc. oftal. hispano-am. 7, 1001 (Oct.) 1947.

Following Gonn's report of his operation for retinal detachment the average rate for cure was about 25 per cent of cases in which his method was used. However, with improvements in the technic, the percentage of recoveries has been gradually increased to the present rate of 70 or 80 per cent of unselected cases. For the last six or eight years this rate has not been improved.

Arruga states that of the 20 or 30 per cent of cases in which operation does not result in improvement, poor results are expected beforehand, for obvious reasons, in approximately one-half, but the other half are cases in which there was confidence in good results, since in similar ones operation had previously been followed with success. In these cases good results were not obtained because of anomalous development of the curative process.

The cases in which the operation was not successful are analyzed under the following heads: (1) detachments anatomicopathologically benign with unfavorable evolution; (2) detachments beginning at the macula; (3) detachments located inferiorly.

The conditions which prevailed to produce poor results after the operation are described.

H. F. CARRASQUILLO

# THE CHANGES OF THE OPTIC NERVE IN NEURO-INFECTIONS. F. YUSEFOVA and Z. GORILOVSKAYA, Vestnik oftal. 26, 11, 1947.

In the Kiev Psychoneurological Institute, during 1945 and 1946, 36 to 40 per cent of the patients admitted had neuroinfections. An analysis of the cases of 80 patients with changes in the optic nerve is given in this paper. There were 35 patients from 10 to 20, 27 patients from 20 to 40 and 18 patients over 40 years of age. Forty patients had encephalitis, 12, encephalomyelitis, 13, meningoencephalitis, and 15 disseminated lesions of the nervous system and polyneuritis. The changes in the optic nerve varied from mild signs, such as engorgement of the veins and hyperemia of the disk (microsymptoms), to marked neuritis, choked disks and pallor of the disk, resulting in optic atrophy. Atrophy of the optic nerve was observed in 26 of 40 patients with encephalitis. Of patients with encephalomyelitis, mild changes of the optic nerve were seen in about one-half, in some, pallor of the disks was observed. The most serious changes in the form of choked disks and optic nerve atrophy (in 12 of 13 patients) were seen in patients with meningoencephalitis.

In patients with microsymptoms, whose vision and visual fields were normal, the blindspot was enlarged and oblong. This, according to Samoilov, is related to retinal edema with accumulation of serum in the perivascular lymph space of the central retinal vein. The enlargement of the blindspot is an early manifestation of the involvement of the optic disk.

O. SITCHEVSKA

## Tumors

CYSTIC MALIGNANT MELANOMA OF THE UVEAL TRACT R E KENNEDY, *Am J Ophth* 31:159 (Feb) 1948

Kennedy reports a case and concludes that cystic malignant melanoma may present a diagnostic problem when it occurs in the posterior chamber, where its differentiation from a benign uveal cyst is difficult. The determination of translucency and the diagnostic puncture may differentiate a solid and a cystic mass in the posterior chamber, but cannot differentiate a benign and a malignant cystic mass. Thus, these diagnostic procedures are unreliable. When accessible, iridectomy and microscopic examination should be used in diagnosis of such lesions when their nature is in doubt.

Large cystic spaces in malignant melanomas arise from the growth of small focal areas of tumor necrosis, which are the result of inadequate nutrition. The cystic manifestation is present in about 8 per cent of all malignant melanomas of the uvea, has no predilection for the site in the uvea or the cell type and has no apparent effect on the prognosis of malignant melanomas.

W S REESE

TWO UNUSUAL SCLERO-CORNEAL NEOPLASMS A LOEWENSTEIN and J FOSTER, *Brit J Ophth* 32:1 (Jan) 1948

In a boy aged 15 years a tumor resembling a phlycten developed at the limbus of the cornea at 11 o'clock. The growth doubled in size in five weeks and when removed was 3.5 mm in diameter. A detailed histologic description of the enucleated eye is presented. The following summary is given. A hard, painless limbal tumor of rapid growth, infiltrating both the cornea and the sclera, with dilated vessels in the overlying conjunctiva, was removed locally. Histologically, this tumor was a spindle cell sarcoma of mature type, unequal cell distribution and a high degree of vascularization, with giant cell formations in the vessel walls. Abundant large mast cells with a big, round nucleus were present. Metachromatic granules filled the cytoplasm of certain fibroblasts and were also seen free in tissues.

As the clinical progress was more rapid than the histologic picture would suggest, the eye was excised. With the slit lamp, a milky film was observed covering the periphery of the retina and continued forward over the ciliary processes. There were no signs of uveitis.

The second case was that of a woman aged 65. The clinical history was obscure. The right eye had been blind about fifteen years. The growth appeared ten years later. On the lower two thirds of the cornea was a cauliflower-like growth, of firm consistency. The eye was enucleated. The neoplasm was a fibroma containing areas of calcareous and myxomatous degeneration arising from a degenerative pannus. Both the growth and the pannus tissue contained mast cells.

It is suggested that the agent producing the metaplasia may be a virus similar to the Shope fibromatous type in wild rabbits.

W ZENTMAYER

FIBROMA OF THE ORBIT A GARCIA MIRANDA, *Ophthalmologica* 113: 149 (March) 1947

The author reports a rare case of fibroma of the orbit and its removal by means of the Kronlein operation. The histopathologic picture is described.

F H ADLER

TRUE GLIOMA OF THE RETINA A HUGGERT and G T HULTQUIST, *Ophthalmologica* 113: 193 (April) 1947

Until now, only 2 cases of true retinal glioma have been reported in the literature. 1 by Dejean (*Arch d'ophth* 51: 257, 1934) and the other by McLean (*ARCH OPHTH* 18: 255 [Aug] 1937). The authors report a case in which they consider one of true glioma or oligodendroglioma in a man of 77 who had had an intraocular tumor for twenty years, which finally necessitated removal of the eye. The tumor was rich in cells and for the most part was made up of medium or small cells, with nuclei fairly rich in chromatin and with varying amounts of cytoplasm. In some places, the cytoplasm was scanty and somewhat dark, but on the whole it was fairly abundant, light and vacuolated, with a darker-staining outer zone. Because of this arrangement, the groups of cells presented a honeycombed appearance. With silver impregnation by the Penfield modification of the method for oligodendroglia, a fair number of argentophilic cell elements with one or more short, sometimes dendritic, processes were observed. No distinct astrocytic elements were observed and there was no filament formation in Holzer preparations. Around the blood vessels there were tumor cells, presenting a pseudorosette arrangement. In its abundance of mitotic figures and extensive areas of necrosis, the tumor diverged somewhat from the general picture typical of oligodendroglioma, but since these features have also been previously observed in brain tumors of this type, the authors believe that this does not militate against the diagnosis of the tumor in their patient.

F H ADLER

UNUSUAL TUMORS OF THE LACRIMAL CARUNCLE M RADNOT, *Ophthalmologica* 113: 270 (May) 1947

Two tumors of the lacrimal caruncle are described. The first occurred in a man aged 69. Histologic examination revealed a cystic tumor, which the author describes as an "oncolytic cyst" derived from an accessory tear gland. The second case occurred in a man aged 67 with a clinical diagnosis of cornu cutaneum. Histologic examination showed a giant cell sarcoma, similar to a perithelioma.

F H ADLER

Uvea

CONCERNING CHOROIDITIS PROLIFERANS CHEN YEN, *Am J Ophth* 31: 207 (Feb) 1948

Yen concludes that choroiditis proliferans seems to be the end result of an exudative, inflammatory detachment of the retina. A hemorrhagic origin can be ruled out almost with certainty. The condition presents a well defined clinical picture.

W S REESE

AN UNUSUAL CASE OF SYMMETRICAL, BILATERAL, NON-TRAUMATIC  
IRIS PROLAPSE M L NAIRAC, Brit J Ophth 31:100 (Nov)  
1947

A Negro woman, aged 22, two weeks prior to consultation felt a strong, burning pain in the right eye, followed by a discharge of "pus" The following day the left eye became similarly affected Both eyes showed a prolapse of the iris between 11 and 1 o'clock The holes in each cornea were clearcut, oval and placed just central to the corneo-scleral junction There was no evidence of inflammation The fundi were normal The whole of the prolapsed iris was cauterized and a thick conjunctival flap placed over the area The probable explanation of the condition is a bilateral acute infection with formation of corneal ulcers, which, with the help of severe blepharospasm and rubbing, perforated quickly and healed

W ZENTMAYER

### Vision

THE COMPARATIVE VISUAL ACUITY AND EASE OF READING IN WHITE  
AND COLORED LIGHT L C MARTIN and R W B PEARSE,  
Brit J Ophth 31:129 (March) 1947

The purpose of the experiments was to obtain information on the relative acuity of an accommodated eye both in red and in white light and on the comparative "ease of reading" The conditions imposed on the work precluded the use of artificial pupils, and binocular vision was used throughout Careful attention was paid to the level of brightness of the visual field and the consequent state of adaption

The general results indicate that, while there is a suggestion of improvement when red light is used rather than white at low levels of illumination, the answer to the question of the influence of chromatic aberration of the eye on acuity cannot be answered with any certainty, owing to the strong influence of intensity on acuity and the uncertainties of heterochromatic photometry

The observation that intensity rather than color was the major controlling factor in acuity in the laboratory experiments suggested that when filters are used in conditions of high illumination acuity of vision might be similarly affected

The most prominent feature of the observations is the loss of acuity with the majority of the filters, the loss is generally greater, the greater the absorption

Tests made to establish the comparative "ease of reading" in red and in white illumination showed that any difference between the two illuminations in their effect on ease or speed of reading is too small to be established with certainty in the present experiments at levels of 0.3 and 6.0 foot candles, though there is indication that "white" light may have some advantage at the higher, and "red" light at the lower, of these two levels

W ZENTMAYER

ANALYSIS OF BINOCULAR VISION J PLICQUE, Ann d'ocul 179:83  
(Feb) 1946

The author discusses the anatomy and physiology of the retina and the cerebral cortex with reference to the phenomena pertaining to binocular vision Then follows a discussion of such topics as the uni-

ocular and binocular perception of depth, aniseikonia and the measurement of stereoscopic vision

The article cannot be adequately summarized and should be read at length to be appreciated

P R McDONALD

OFFICIAL CONTROL OF COLOR VISION IN SWEDEN C G BOSTROM and I KUGELBERG, *Ophthalmologica* 114: 95 (Aug) 1947

The official color tests in Sweden are made with the new pseudochromatic charts produced by Bostrom and Kugelberg, as well as the older ones of Gothlin and Bostrom. The Ishihara and Stilling charts are no longer used, having been proved unreliable. If there is any abnormality of color sense, a second test is made with a spectrum

F H ADLER

FUSION FREQUENCY WITH INTERMITTENT LIGHT UNDER VARIOUS CIRCUMSTANCES B S HYLKEMA, *Acta ophth* 20: 159, 1942

The author's summary, in part, is as follows

An investigation of the fusion frequency was made at various light intensities, especially at high intensities. In the fusion frequency-intensity curve, a peak is formed in the area of from 200 to 800 candle powers per square meter. It may be that this luminosity is the optimum for visual function, and perhaps the determination of fusion frequency can be used to ascertain ideal lighting conditions

O P PERKINS

### Visual Tracts and Fields

MEASUREMENT OF THE CONDUCTABILITY OF THE CENTRAL OPTIC PATHWAY BY MEANS OF COMBINED ELECTRORETINOGRAPHY AND ELECTROENCEPHALOGRAPHY M MONNIER and R L JEANNERET, *Ophthalmologica* 113: 1 (Jan) 1947

Simultaneous electroretinographic and electroencephalographic studies on human subjects enable the authors to divide "blocking time" of the alpha rhythm into two periods. The duration of the first (retinal time) extends from the onset of the light stimulation to the moment the impulses are discharged into the optic nerve. It corresponds to the latent period of potential b of the electroretinogram and varies with the intensity of the stimulation. The authors measured the retinal latent period and obtained a mean in the normal subject of 45 milliseconds. The second period (postretinal, or central, time) lasts 124 milliseconds in the normal subject. It corresponds to the conduction time of the impulses within the central optic pathways and is independent of the intensity of stimulation.

In a patient with tabetic atrophy of the optic nerve, the authors found a longer conduction time, namely 225 milliseconds in the right eye and 264 milliseconds in the left eye. These values were subject to greater variations in the patients with tabetic atrophy than in the normal subjects. The significance of these changes is discussed

F H ADLER

**Sympathetic Ophthalmia**

SYMPATHETIC OPTIC NEURITIS REPORT OF A CASE LEGROUX, Arch  
d'opht 6:43, 1946

The case was that of a boy aged 15 who lost his left eye as the result of an accident. On first examination the eye was atrophic, it was enucleated but, unfortunately, was not examined histologically. Vision in the right eye was reduced to 0.10. The media were clear, and the nerve head presented the appearance of neuritis. The iris was normal. In the course of treatment a decompression of the sphenoid bone was done, after this, notable improvement in vision took place. Treatment consisted also of administration of sodium salicylate.

S B MARLOW

## Book Reviews

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**Strabismus—A Clinical Handbook** By George J Epstein Price, \$5 00 Pp 224, with 123 illustrations Philadelphia The Blakiston Company, 1948

That this is the third book dealing with the ocular muscles to appear within a year points to the renewed interest in strabismus. The present volume has much to recommend it to all students, regardless of their degree of experience.

The section on anatomy and physiology of the extraocular muscles is generally good. There are a few minor mistakes which should be corrected in subsequent editions. Illustration 5, of the torsional movements of the globe, and the text on page 9 are incorrect. If movements of the right eye are considered alone, on looking up and to the right and on looking down and to the left, the right eye undergoes extorsion. On looking up and to the left or down and to the right, the eye undergoes intorsion. The after-images should occupy the same positions and correspond in their tilt to the tilt of the vertical meridian of the eye. Illustration 6, on page 10, is also wrong. It is stated that the figure was taken from Duke-Elder's "Text-Book of Ophthalmology," but it does not correspond to figure 583 in Duke-Elder's first edition, volume I, which illustration is correct.

Some sections of the book, particularly the physiology of binocular vision and those parts which deal with retinal correspondence, will not be acceptable to all students of squint. The author states that in monocular concomitant esotropia the phenomenon of monocular anomalous retinal correspondence "is always present," and that in alternating concomitant esotropia, alternating anomalous retinal correspondence "is always present." Just what is meant by "monocular" and "alternating anomalous correspondence" is not clear to the reviewer. The author can hardly mean to imply that all cases of concomitant strabismus have anomalous retinal correspondence. It would seem that he has this idea, however, since he describes normal retinal correspondence as a "sensory state existing in cases of normal muscle balance" and says, further, that when strabismus supervenes this state is altered and the alteration is known as anomalous retinal correspondence. This is an unorthodox point of view.

The author firmly believes that concomitant strabismus generally arises from a congenital muscle paresis and that the most common muscle affected with congenital paralysis is the superior rectus. This is another subject about which there has been much debate. The sections on treatment, especially the surgical treatment of strabismus, are clear and concise. The book is very readable. The style is reminiscent of Chavasse and therefore contrasts favorably with many of our American texts, in which the style is generally not fluent and is frequently awkward.

FRANCIS H ADLER

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